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Venetoclax-based therapies for acute myeloid leukemia

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ABSTRACT

The prognosis of adult acute myeloid leukemia (AML) remains poor, with the long-term survival rate less than 50%. However, the current paradigms of treatment are changing through a better understanding of the disease genetics and pathophysiology. Since 2017, eight new drugs have been approved by the U.S. Food and Drug Administration for the treatment of AML, including the FLT3 inhibitors midostaurin and gilteritinib, the IDH inhibitors ivosidenib and enasidenib, the anti-CD33 monoclonal antibody gemtuzumab ozogamicin, liposomal daunorubicin and cytarabine, the hedgehog pathway inhibitor glasdegib and the BCL-2 inhibitor venetoclax. Preclinical data demonstrated the anti-leukemic efficacy of venetoclax in AML and its synergy when combined with hypomethylating agents or chemotherapy agents. Clinical trials have demonstrated the clinical benefit of venetoclax-based therapies in newly diagnosed AML, leading to the recent FDA approval of venetoclax in combination with hypomethylating agents or low-dose cytarabine for older adults with newly diagnosed AML. Herein, we focus on the role of single-agent BCL-2 inhibition in AML and review the clinical studies of venetoclax-based combination regimens and the evolving mechanisms of resistance.

Introduction

Acute myeloid leukemia (AML) is a heterogeneous hematopoietic neoplasm characterized by rapid clonal proliferation of immature hematopoietic cells with different degrees of differentiation toward myeloid lineage. It affects approximately 4.3 adults per 100,000 per year in the U.S., with a median age at diagnosis of 68 years [1].

The standard therapy for *de novo* AML consists of induction chemotherapy with an anthracycline agent in combination with the nucleoside analog, followed by consolidation therapy with high-dose cytarabine regimens or hematological stem cell transplant (HSCT) [2]. Despite high rates of complete response (CR) of over 80% in younger adults (< 65 years) and between 40% and 60% in older adults (≥65 years), the cure rates remain poor, with a rate of long-term survival 5 years after diagnosis of only 40–50% for younger adults and less than 10% for older adults [3–5]. Despite recent advances and new targeted therapies, the management of AML remains a challenge, particularly in older adults ineligible for intensive therapies. The overexpression of the anti-apoptotic proteins B-cell lymphoma-2 (BCL-2) and MCL-1 has been associated with therapy resistance of AML cells [6]. BCL-2 inhibitors such as venetoclax and novel MCL-1 inhibitors have shown anti-leukemic activity in preclinical AML models. This review focuses on the role of the BCL-2 inhibitor venetoclax in the management of adult AML. We summarize the results of studies combining venetoclax with low-intensity regimens in relapsed/refractory and *de novo* AML, ongoing clinical trials and emerging mechanisms of resistance to venetoclax.

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BCL-2 family proteins and apoptosis regulation

The BCL-2 family of proteins consists of pro-apoptotic and anti-apoptotic molecules that can be classified into three main groups according to protein function and homology. The anti-apoptotic proteins comprise BCL-2, BCL-XL or BCL2-L1, MCL-1 and BCL-W with BCL-2 homology (BH) in all four regions (BH 1–4); the pro-apoptotic proteins, BAX and BAK with BH in regions 1–3; and the BH3–only proteins, BIM, NOXA, PUMA, BMF, BAD, HRK, BIK and BID. The translocation of pro-apoptotic proteins BAX and BAK induces mitochondrial outer membrane permeabilization and cytochrome c release, followed by caspase activation and apoptotic cell death. BH3–only proteins BID and BIM promote mitochondrial permeabilization by activation of BAX and BAK, while sensitizer BH3 proteins BAD, BIK, PUMA and BMF bind and oppose activation of anti-apoptotic proteins [7,8]. In contrast, BCL-2 and BCL-XL prevent BAX/BAK-dependent mitochondrial outer membrane permeabilization by both direct inactivation of BAK and BAX and by sequestration of BH3–only proteins [9,10]. Fig. 1 summarizes the mitochondrial pathway of apoptosis and the role of the BCL-2 family of proteins.

Venetoclax is an oral highly selective BCL-2 inhibitor that has shown activity in BCL-2–dependent haematologic malignancies, particularly in chronic lymphocytic leukemia (CLL) [11,12]. It was granted accelerated approval by the U.S. Food and Drug Administration (FDA) for CLL with 17p deletion in April 2016 and was later approved in June 2018 for CLL with or without 17p

Fig. 1. Mitochondrial pathways of apoptosis and venetoclax mechanism of action. In response to cellular stress, the pro-apoptotic proteins BAX and BAK are translocated to the mitochondria and induce the permeabilization of the outer mitochondrial membrane with release of cytochrome c (Cyt C) into the cytoplasm. The Cyt C/Apaf-1 complex activates caspase 9 and the caspase cascade, inducing apoptosis. The mitochondrial pathway is regulated by pro-apoptotic BH3-only proteins, which activate BAX and inhibit BCL-2 and MCL-1. BCL-2, MCL-1 and BCL-X regulate cell survival by inactivation of the pro-apoptotic proteins. Venetoclax triggers apoptosis by selective inhibition of BCL-2, leading to the release of Cyt C and cell death.

Table 1
Summary of clinical activity of venetoclax combination regimens in treatment-naïve and relapsed/refractory AML.

Combination	Ven mg	Phase/Study	Population	N	Age [range]	CR/CRi rate	MRD (−)	DOR	OS
LDAC [19]	600	I/II	Frontline	82		54% ND 71% s-AML 35%		8.1 m 11.6 m 8.1 m	10.1 m
HMA [20]	400–1200	Ib	Frontline	145	74 [65–86]	67% ND 67% s-AML 67% VEN 400 73% VEN 800 65%	29%	11.3 m 12.5 m NR 12.5 m 11 m	17.5 m 12.5 m NR NR 17.5 m
5 + 2 [30]	50–600	Ib	Frontline	44	72 [63–80]	71% ND 95% s-AML 42%			
LDAC [66]	100–200	Retrospective	Frontline AML, MDS, CMML	19	77 [64–87]	52.6%			NR 61% at 6 m
DAC-10 [29]	200–400	II	Frontline R/R AML	48	> 60	R/R 44% ND 71% s-AML 71%	50% 52% 40%	3.3 m NR NR	NR NR NR
HMA [34]	50–800	Retrospective	Frontline R/R AML	42	67 [25–88]	43% ND 33% s-AML 50% R/R 40%			6.2 m 5.8 m 8.8 m 6.6 m
HMA [28]	200–400	Retrospective	Frontline R/R AML	107	68 [19–86]	53% ND 61% R/R 48%	64%		12.5 m 14.6 m (CR)
HMA/LDAC [35]	400–800	Retrospective	R/R AML	24	66 [29–85]	28.6%	9.5%		72% at 3 m.
HMA/LDAC [33]	100–800	Retrospective	R/R AML, MDS, BPDCN	43	68 [25–83]	21%			3 m 4.8 m (CR)
HMA/LDAC [36]	100–800	Prospective	R/R AML	22	76 [41–92]	41%			5.5 m 12.5 m (CR)
FLAG-IDA [31]	200	Ib/II	R/R AML	12	49 [32–72]	73%		NR	67% at 6 m.
Cobimetinib or idasanutlin [55]	400–800	Ib	R/R AML s-AML	42	72 [60-92	Cobimetinib 18% Idasanutlin 20%		1–5 m 1.3–6.7 m	

Abbreviations: AML, acute myeloid leukemia; Ven, venetoclax; CR, complete response; CRi, complete response with incomplete hematological recovery; MRD, minimal residual disease; DOR, duration of response; OS, overall survival; LDAC, low-dose cytarabine; ND, newly diagnosed; s-AML, secondary AML; m, months; HMA, hypomethylating agent; NR, not reached; 5 + 2, 5-day cytarabine and 2-day idarubicin; MDS, myelodysplastic syndrome; CMML, chronic myelomonocytic leukemia; DAC-10, 10-day decitabine, R/R, relapsed/refractory; BPDCN, blastic plasmocytoid dendritic cell neoplasm; FLAG-IDA, fludarabine, cytarabine, idarubicin, granulocyte colony–stimulating factor.

deletion, following at least one prior therapy [13,14]. Preclinical studies demonstrated induction of AML cell death by BCL-2 inhibition in primary AML samples *in vitro* and in xenograft models *in vivo* and synergistic anti-leukemia activity when combined with an HMA, with negligible effects on platelets compared to previous BH3 mimetics [15–17].

Venetoclax as single-agent therapy for AML

The first Phase II trial of Venetoclax was as a single-agent for relapsed/refractory AML or for AML unfit for intensive chemotherapy [18]. Thirty-two patients received venetoclax at a dose of 400 mg or 800 mg daily with dose escalation to 1200 mg for patients whose tumor did not respond; the median age of these 32 patients was 71 years (range 19–84), and 94% had received at least one prior therapy. IDH1/2 and FLT3-ITD mutations were present in 38% and 13% of the tumors, respectively. The CR/CR with incomplete haematologic recovery (CRi) rates were 19%, and an additional 19% of patients showed a partial bone marrow response. Most of the patients with CR/CRi had reached that response by week 4 of therapy. For patients with prior HMA exposure, the CR/CRi rate was 25% (6/24). Patients with an IDH1/2-mutant tumor showed a higher CR/CRi rate of 33%. The higher dose of 1200 mg did not yield additional responses. No tumor lysis syndrome was reported.

Single-agent venetoclax was well tolerated but had limited anti-leukemic activity in relapsed/refractory AML, with leukemia-free survival and OS rates of 2.3 months and 4.7 months, respectively. The low response rates with short response duration prompted further studies of regimens combining venetoclax with other agents which had demonstrated synergy in pre-clinical studies. These trials were conducted in older patients (aged 65 years or older), with previously untreated AML unfit for intensive induction chemotherapy. Table 1 summarizes the results of the combination studies with venetoclax in relapsed/refractory and newly diagnosed AML.

Combination clinical studies with venetoclax in AML

Clinical studies in newly diagnosed AML

A Phase Ib/II clinical study evaluated the combination of venetoclax with LDAC in older adults with newly diagnosed AML unfit for intensive regimens [19]. A total of 82 patients were enrolled to receive cytarabine 20 mg/m^2/daily for 10 days with venetoclax 600 mg once daily for 28 days. Venetoclax was given in a 5-day ramp-up for the first cycle. Thirty-two percent of the patients had poor-risk cytogenetics, and 49% had secondary AML, 60% of those with prior HMA exposure. The therapy was well tolerated, with the most common grade 3 adverse events being cytopenias and infections. Only two cases of laboratory grade 3 tumor lysis syndrome were reported. The CR/CRi rate was 54%, with a median time to response of 1.4 cycles, and the rate of minimal residual disease (MRD) negativity was 32% by flow cytometry ($< 10^{-3}$). A higher response rate was achieved in patients with *de novo* AML, with a CR/CRi rate of 71% and a duration of response (DOR) of 11.6 months; corresponding results in patients with secondary AML were 35% and 8.1 months, respectively. Patients with NPM1 or IDH1/2 mutation showed the greatest response, with CR/CRi rates of 89% and 72%, respectively, compared to 30% and 44% for patients with TP53 or FLT3 mutation. Overall, the median OS was 10.1 months with an estimated 1 year OS of 27%

In a multicentre Phase Ib study, venetoclax was tested in combination with HMA therapy, decitabine or azacitidine, in elderly patients with newly diagnosed AML who were unable to receive intensive therapy [20]. Three venetoclax dose levels of 400 mg, 800 mg and 1200 mg were explored, and the 400 mg and 800 mg cohorts were tested further in dose expansion cohorts due to optimal safety and efficacy profiles [21]. Overall, 174 patients were enrolled, with a median age of 74 years (range 65–86). Mutations present in this cohort included TP53 (25% of patients), FLT3 (12%), IDH1/2 (24%) and NPM1 (16%). Twenty-five percent had secondary AML, and 49% had adverse cytogenetics. During the expansion phase, patients were randomised to receive venetoclax 400 mg or 800 mg with either decitabine 20 mg/m^2 for 5 days or azacitidine 75 mg/m^2 for 7 days every 28 days. The treatment was well tolerated, the most common side effects being any grade nausea (58%), constipation (52%), neutropenia (31%) and diarrhea (47%), and the most common grade 3-4 adverse events were infections (45%), pneumonia (18%), fungal infections (8%) and sepsis (10%). Nonetheless, the 30-day early mortality was low (3%), and no cases of tumor lysis syndrome were reported. With a median follow-up duration of 15 months, the overall CR/CRi rate was 68%, with a median time to response of 1.2 cycles and a rate of MRD negativity by flow cytometry of 29% among the patients who showed a response. No difference in response rate was observed between the venetoclax 400 mg and 800 mg groups ($p = 0.35$). Overall, 21 patients proceeded to HSCT, and 70% discontinued therapy.

Responses were seen in all subgroups, with higher response rates in the patients whose tumor expressed mutant IDH1/2, NPM1 or FLT3, with CR/CRi rates of 71%, 91% and 72%, respectively, than in patients whose tumor had a TP53 mutation (CR/CRi rate 47%). The responses were durable in patients with a IDH1/2 or NPM1 mutation, with DOR not reached; DOR was 11 months for patients with a FLT3 mutation and much shorter, 5.6 months, for patients with a TP53 mutation. The multivariable analysis confirmed NPM1 mutation as a predictor of favorable outcome compared to wild type NPM1 ($p = 0.049$). In all patients treated, the median DOR and OS were 13.1 months and 17.5 months, respectively, and DOR and OS were not reached in the azacitidine and venetoclax 400 mg subgroup.

In summary, the studies of combined venetoclax with low-dose cytarabine or with an HMA demonstrated high response rates with durable responses and longer OS in elderly adults with previously untreated AML compared to the historical 10–20% CR/CRi rates and median OS of 5–7 months with LDAC and 6–10 months with an HMA [19,20,22–26].

Based on these results, in November 2018 venetoclax was approved by the FDA in combination with an HMA (azacitidine or decitabine) or low-dose cytarabine for newly diagnosed AML or AML ineligible for intensive chemotherapy in adults aged 75 years

and older [27]. Two combinations (venetoclax 400 mg in combination with azacitidine, NCT02993523; and venetoclax 600 mg in combination with low-dose cytarabine, NCT03069352) are currently undergoing definitive randomised Phase III studies for newly diagnosed AML in elderly patients unfit for intensive therapies, with OS as a primary objective.

Other studies of venetoclax in combination with hypomethylating agents

Aldoss et al. reported similar results with venetoclax in combination with an HMA (decitabine or azacitidine) for newly diagnosed or relapsed/refractory AML [28]. In that trial, 107 patients with a median age of 68 years were treated with venetoclax 400 mg and 10 days of decitabine on a 28-day cycle. Patients received venetoclax daily for 28 days during the first cycle, followed by 21 days of venetoclax for subsequent cycles. Of those, 57% had relapsed/refractory AML and had received a median of 2 prior therapies. The overall CR/CRi rate was 53% after a median of 2 cycles, with a 64% rate of MRD negativity by flow cytometry. Similar to previous reports, the CR/CRi rate in patients with newly diagnosed AML was 61%; among patients with relapsed/refractory AML, 48% had a CR/CRi. In the ongoing study, high response rates were reported in the cohort with newly diagnosed AML, including patients whose tumor expressed a TP53 mutation [29].

Venetoclax combinations with chemotherapy

The role of venetoclax in the frontline setting for “fit” older patients eligible for intensive chemotherapy is being evaluated in an ongoing Phase Ib study, CAVEAT [30]. Patients received venetoclax with dose-reduced intensive chemotherapy (5 + 2). Of the 44 patients enrolled, 41% had secondary AML and 38% previous exposure to an HMA. The median age was 72 years (range 63–80). Venetoclax was evaluated in dose escalation cohorts of 50 mg–600 mg daily for 14 days with a 7-day dose ramp-up followed by cytarabine 100 mg/m^2 for 5 days and idarubicin 12 mg/m^2 for 2 days during induction. Patients whose disease achieved remission received 4 cycles of a consolidation regimen comprising venetoclax for 14 days, cytarabine 100 mg/m^2 for 2 days and idarubicin 12 mg/m^2 for 1 day, followed by maintenance therapy with single-agent venetoclax for 14 days every 28 days for 7 cycles. The overall CR/CRi rate was 71%; as expected, it was higher (95%) in patients with newly diagnosed AML and lower (42%) in those with secondary AML. Patients with adverse cytogenetics or prior exposure to an HMA had lower response rates (46% and 43%, respectively). As observed in other studies, response rates were over 90% in patients with a NPM1, RUNX1, RAS or IDH mutation but only 33% in patients with a TP53 mutation. No tumor lysis syndrome was reported. These interim results confirm the safety of the combination of venetoclax up to 600 mg with cytarabine and idarubicin induction chemotherapy for fit elderly AML patients.

A combination of the FLAG-IDA (fludarabine, cytarabine, idarubicin, granulocyte colony–stimulating factor) regimen with venetoclax is currently being evaluated in adults with relapsed/refractory AML eligible for intensive therapy in a Phase Ib/II clinical study [31]. In the initial dose-finding cohort, patients received fludarabine 30 mg/m^2 daily from days 2–6, cytarabine 2 g/m^2 daily from days 2–6, idarubicin 6 mg/m^2 daily from days 4–6 and granulocyte colony–stimulating factor5 mcg/kg daily for 7 days (or one dose of PEG-filgrastim) in combination with venetoclax 200 mg for 21 days, with a 2-day ramp up, on a 28-days cycle. Due to high responses but increased adverse events including neutropenic fever, bacteremia and sepsis, the protocol was amended to reduce the duration of venetoclax to 14 days and reduce the dose of cytarabine to 1.5 g/m^2. After induction and consolidation therapy, patients who were not candidates for HSCT could continue maintenance therapy with venetoclax 400 mg daily. Preliminary results from the Phase 1 portion were presented at ASH 2018 and demonstrated efficacy with 73% (8/11) patients with CR/CRi, all but one occurring within the first cycle, with a median time to neutrophil recovery of 28 days (23–33 days). While 30 and 60 day mortality was zero, significant adverse events included gram-negative bacteremia (42%), infections and sepsis (33%), requiring hospitalization and intravenous antibiotics which led to the dose adjustments described above. To date with a median follow-up reported of 4 months, the median DOR has not been reached, with a 6-month OS rate of 67%, and patient accrual of two cohorts (newly diagnosed AML and relapsed/refractory AML) is ongoing in Phase II.

Clinical studies with venetoclax in relapsed/refractory AML

The combination of venetoclax with an HMA or LDAC was further evaluated in relapsed/refractory AML, myelodysplastic syndrome (MDS) and blastic plasmacytoid dendritic cell neoplasm (BPDCN), but these were limited to retrospective reports [32–36]. In a retrospective analysis conducted at MD Anderson Cancer Center, 43 patients with a median age of 68 years (range 25–83) were treated with venetoclax in combination with low-intensity therapy [33]. These patients were heavily pre-treated, with high-risk features: 77% had received a prior HMA, 84% had received at least 2 prior therapies, (median 3) and 47% had adverse cytogenetics. Venetoclax was given at doses between 100 mg and 400 mg (median 300 mg), with dose reductions when administered with a CYP3A4 inhibitor. Most patients received venetoclax in combination with an HMA, decitabine (53%) or azacitidine (19%), while 19% received LDAC. Twenty-one percent had an objective response after one cycle, 12% CR/CRi and 9% morphologic leukemia-free state. The median OS was 3 months, with an estimated 6-month OS rate of 24% for responders. Notably, the objective response rate was 24% (5/21) in patients with diploid/intermediate-risk cytogenetics, 27% (3/11) in those with an IDH1 or IDH2 mutation, 50% (4/8) in those with a RUNX1 mutation and 15% (3/20) in those with adverse cytogenetics. The most frequent adverse effects were prolonged cytopenias and infections, with no tumor lysis events. While response rates were modest, the combination of venetoclax with low-intensity chemotherapy was demonstrated to be safe and well tolerated, offering an alternative therapy for patients with relapsed/refractory AML, particularly those with diploid/intermediate-risk cytogenetics or IDH1, IDH2 or RUNX 1 mutation.

Concomitant used of antifungal prophylaxis

Venetoclax is metabolized by cytochrome P450 3A4 and drug-drug cytochrome P450 interactions have been reported with moderate and strong CYP34A inhibitors, including antifungal agents. Co-administration with posaconazole induced 7.1- to 8.8-fold increases of venetoclax Cmax and AUC due to decreased clearance and increased accumulation of venetoclax [37,38]. A 75% dose reduction of venetoclax is recommended for patients treated with strong CYP3A inhibitors, such as voriconazole or posaconazole and a 50% reduction with the moderate CYP3A inhibitors fluconazole and isavuconazonium sulfate. The FDA recommendation is to dose reduced venetoclax to 70 mg when administer alongside with posaconazole.

Mechanisms of resistance to BCL-2 inhibition

Overexpression of the anti-apoptotic proteins BCL2-A1, BCL-XL and MCL-1 has been associated with increased tumor cell survival, chemoresistance and resistance to the BCL-2 inhibitor venetoclax [6,18,39,40]. Lower BCL2-A1 levels; PML-RARA translocation; WT1, FLT3 and IDH1 mutations have been reported to confer higher sensitivity to venetoclax; in contrast, TET2, KRAS, PTPN11 and SF3B1 mutations have been linked to resistance [40].

While BCL-2 expression does not strictly predict antitumor response to BCL-2 inhibition, sensitivity is determined by the amount of BCL-2 actively binding and sequestering pro-apoptotic proteins, also known as priming [41]. Highly BCL-2 primed cells are more susceptible to BCL-2 inhibitors, and the exposure of un-primed or normal cells to venetoclax does not induce apoptosis. BCL-2 priming can be evaluated by BH3 profiling, which measures mitochondrial outer membrane permeability after exposure of tumor cells to BH3-containing proteins. It allows parsing of tumor addictions to specific BCL-2 family protein(s) and can predict tumor cell sensitivity or resistance to selective BCL-2 inhibitors such as venetoclax [18,42,43].

Another potential target for overcoming venetoclax resistance is the anti-apoptotic protein MCL-1, which is highly expressed in AML. Preclinical studies have shown that venetoclax has synergistic activity with MCL-1 inhibitors [44–48]. More recent data also indicate synergy with inhibitors of cyclin-dependent kinase 9 (CDK9) such as AZD4573 [6], through transcriptional downregulation of MCL-1, with MDM2 inhibitor Idasanutlin through Mcl-1 degradation and with ONC213 analog imipridone through MCL-1 decrease [49,50]. Several studies are now evaluating venetoclax in combination with apoptosis regulators such as the CDK9 inhibitors dinaciclib (NCT03484520) and alvocidib (NCT03441555) in relapsed/refractory AML.

Future directions

Novel combinations with venetoclax are currently under investigation, such as CDK inhibitors, IDH1 and IDH2 inhibitors, mitogen-activated protein kinase 1 (MAP2K1 or MEK1) inhibitors, mouse double minute 2 homolog (MDM2) antagonists and FLT3 inhibitors. CDK inhibitors regulate the cell cycle by blocking thymidine DNA incorporation, and they additionally induce cell death by downregulating the pro-apoptotic proteins MCL-1 and BCL-2 [51,52]. MEK1 inhibitors such as cobimetinib downregulate MCL-1 by inactivation of the RAF/MEK/ERK pathway, which normally stabilizes MCL-1 [53]. Padua et al. demonstrated *in vitro* anti-leukemic activity of venetoclax and the MEK1 inhibitor GCD-0973 against MDS/AML progenitors through inhibition of the RAS/BCL-2 complex, even in venetoclax- or MEK inhibitor–resistant samples [54]. MDM2 antagonism disrupts MDM2-TP53 interactions and mediates cell death by activating the TP53 pathway. Preclinical data indicate striking synergy in co-targeting the BCL-2 and MDM2/p53 pathways, through induction of BH3-only proteins downstream of p53 activation and inhibition of MCL-1 through the RAS/MAPK pathway [50]. An ongoing Phase I/Ib clinical trial is testing tolerability and activity of combinations of venetoclax plus MEK1 inhibitor cobimetinib or MDM2 inhibitor idasanutlin in relapsed/refractory AML in elderly patients (NCT02670044), and early results indicate clinical activity of the idasanutlin/venetoclax combination with an ORR of 38% [55].

IDH mutations predicted higher rates of response to BCL-2 inhibition through production of 2-hydroxyglutarate (2-HG) and inhibition of cytochrome c oxidase activity, making AML cells dependent on Bcl-2 for survival, as cytochrome c oxidase inhibition increases activation of the BAX/BAK complex [56,57]. In clinical trials, tumors expressing an IDH1 or IDH2 mutation appear to be particularly sensitive to BCL-2 inhibition, with corresponding higher rates of response and long-term survival [18,20]. IDH2 inhibition reduces 2-HG levels, causes leukemia cell differentiation and has shown anti-leukemic activity in IDH2-mutated AML, both in preclinical studies and in clinical trials [58–62]. Since IDH inhibition reduces 2-HG, a main mediator of BCL-2 dependence, there was an initial concern of possible antagonistic interactions upon concomitant BCL-2 and IDH blockade. However, a recent preclinical study showed that the combination of enasidenib and venetoclax had synergistic anti-leukemic efficacy *in vivo* AML patient-derived xenograft models of IDH2-mutated AML, possibly because of blast cell differentiation and reduction of the anti-apoptotic proteins [57]. In an ongoing Phase I/II clinical trial, the tolerability and clinical activity of combined venetoclax and IDH1 inhibitor ivosidenib is being tested in patients with IDH1-mutated AML (NCT03471260).

FLT3-ITD mutations are associated with lower response to venetoclax as a single agent and possibly in combination, in part due to upregulation of the MCL-1 protein; in turn, FLT3 and BCL-2 inhibition were shown to work in concert [63,64]. Recent findings suggest that the occurrence of a newly discovered D835 mutation may correlate with resistance to tyrosine kinase inhibitors in FLT3-ITD-mutant AML by overexpression of BCL-2 and induction of anti-apoptotic signalling, which translates to higher responsiveness to venetoclax [65]. Clinical trials are evaluating the combination of venetoclax with the tyrosine kinase inhibitors gilteritinib (NCT03625505) and quizartinib (NCT03735875) for relapsed/refractory AML with FLT3 mutation. Table 2 summarizes the venetoclax-based studies ongoing in AML.

Table 2
Summary of ongoing clinical trials with venetoclax in combination therapy for adults with treatment-naïve or relapsed/refractory adult AML.

Combination regimen	Chemotherapy/targeted agent	Trial Phase	Population	Age (years)	Clinicaltrials.gov Identifier
AZA vs. AZA alone	HMA	III	Frontline AML	≥18	NCT02993523
LDAC vs. LDAC alone	Chemotherapy	III	Frontline AML	≥18	NCT03069352
Daunorubicin + cytarabine	Chemotherapy	I	Frontline AML	18–75	NCT03709758
Cladribine, LDAC, azacitidine	Chemotherapy/HMA	II	Frontline AML	< 60	NCT03586609
Azacitidine	HMA	II	Frontline AML	18–59	NCT03573024
Azacitidine	HMA	II	Frontline AML	≥60	NCT03466294
10-day decitabine	HMA	II	R/R AML/HR-MDS	≥18	NCT03404193
			Frontline AML/HR-MDS	≥60	
FLAG-IDA	Chemotherapy	I/II	R/R AML	≥18	NCT03214562
			Frontline AML	≥18	
CPX-351	Chemotherapy	II	R/R AML	≥18	NCT03629171
			Frontline AML	18–59	
Dinaciclib (MK7965)	CDK9 inhibitor	I	R/R AML	≥18	NCT03484520
Alvocidib	CDK9 inhibitor	I	R/R AML	≥18	NCT03441555
Cobimetinib or idasanutlin	MEK1 inhibitor/MDM2 inhibitor	I/II	R/R AML	≥60	NCT02670044
Gilteritinib	FLT3 inhibitor	I	R/R AML FLT3+	≥18	NCT03625505
Quizartinib	FLT3 inhibitor	I/II	R/R AML FLT3+	≥18	NCT03735875
Ivosidenib (AG120)	IDH1 inhibitor	I/II	R/R AML IDH1+	≥18	NCT03471260
			Frontline AML/HR-MDS IDH1+		

Abbreviations: AML, acute myeloid leukemia; AZA, azacitidine; HMA, hypomethylating agent; LDAC, low-dose cytarabine; R/R, relapsed/refractory; HR-MDS, high-risk myelodysplastic syndrome; FLAG-IDA, fludarabine, cytarabine, idarubicin, granulocyte colony–stimulating factor.

Summary

The management of adult AML is rapidly changing to an individualized approach with the application of target-directed therapies adapted to the specific characteristics of the leukemia. The genetic alterations and mutation patterns not only allow for better characterization of disease prognosis but also become determinants in AML management. High response rates and longer responses were seen when combining BCL-2 inhibitor venetoclax and low-intensity therapies in AML patients, even in the relapsed/refractory setting. AML cells were shown to be particularly dependent on BCL-2 for their survival, at least in part agnostic of mutational profiling, which provides opportunities for synergistic combinatorial therapies. The recent approval of venetoclax in combination with HMAs and low-dose intensity chemotherapy will significantly change the therapeutic landscape, becoming a standard of care in elderly patients and for the first time extending survival.

Further research is needed to determine the role of venetoclax added to high-intensity chemotherapy or possibly pre-transplant conditioning for younger adults. Direct or indirect co-targeting of MCL-1 appears to facilitate responses to these strategies and is currently being exploited in combinations of venetoclax with FLT3-ITD, MDM2, MEK and CDK9 inhibitors, as well as direct MCL-1 inhibitors that recently entered the clinical arena. Concomitant blockade of IDH1/IDH2 in IDH1/2 mutated patients could cause both differentiation and death of AML blasts, leading to durable responses. Finally, venetoclax alone or in combinations with an HMA could be considered a viable and safe maintenance option in high-risk AML patients completing consolidation therapies or after HSCT.

Practice points

- Advances in the understanding of the genetic alterations and mutations in AML have led to the development of novel targeted therapies, such as FLT3 and IDH1/2 inhibitors, and have changed the standard of care. AML therapies should be tailored to the specific characteristics of each patient's leukemia.
- Combinations of venetoclax with low-dose cytarabine or a hypomethylating agent have shown high response rates and prolonged overall survival in elderly AML patients unfit for standard intensive chemotherapy.
- Venetoclax therapy alone and in combinations is well tolerated, with the most common adverse effects being neutropenia, infections and gastrointestinal toxic effects.
- Treatment interruptions are uncommon and are often related to prolonged neutropenia and infections, warranting reductions of venetoclax duration or dose.
- Frequency of tumor lysis syndrome is less than 5% in AML when using venetoclax in a rapid ramp-up fashion and limiting pre-treatment white cell count/tumor burden.
- As venetoclax is metabolized by CYP3A4, dose reductions are recommended when co-administered with strong or moderate CYP3A4 inhibitors.
- With the combination of venetoclax with low-dose cytarabine or hypomethylating agents bone marrow assessment is recommended at the end of the first cycle (i.e. day 21-day28), with potential interruption as early as day 21 if CRi or morphological leukemia-free status is obtain to allow for count recovery prior to starting cycle 2. We recommend an absolute neutrophil (ANC) recovery ≥ 500/μl, and growth factors may be used if no ANC recovery is seen after two weeks. If therapy interruptions are

required in subsequent cycles for ongoing cytopenias or other complications in the setting of response, venetoclax duration can be reduced.

- Patients treated with combination venetoclax and intense chemotherapy should be closely monitored with appropriate antibacterial, antifungal and antiviral prophylaxis, as prolonged myelosuppression could increase the risk of severe infections and sepsis.

Research agenda

- MCL-1 overexpression is associated with tumor cell resistance to chemotherapy, BCL-2 inhibition and tumor cell survival. Several new targeted agents have shown anti-leukemia effects by downregulating MCL-1 levels and increasing tumor cell apoptosis. Future research should focus on the tolerability and efficacy of MCL-1 modulators in combination with BCL-2 inhibitors in AML.
- Further studies are warranted to evaluate the role of venetoclax with or without an HMA as maintenance after HSCT in AML

Disclosure of conflicts of interest

The authors have no relevant conflicts of interest to disclose.

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