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PERSPECTIVE

Acute myeloid leukemia

How we use venetoclax with hypomethylating agents for the treatment of newly diagnosed patients with acute myeloid leukemia

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Abstract

Acute myeloid leukemia (AML) is associated with poor outcomes, especially in older patients in whom the disease is most common. B-cell lymphoma 2 (BCL-2) is an antiapoptotic protein involved in the survival and maintenance of AML, and it is overexpressed in the leukemia stem cell population. Venetoclax is an oral BCL-2 protein inhibitor recently approved by the United States Food and Drug Administration (FDA) for use in combination with a hypomethylating agent (HMA) (azacitidine or decitabine) or low-dose cytarabine for front-line treatment of AML in older patients or those unfit for induction chemotherapy. Given that its mechanism of action is unique, it is not surprising that this widely effective therapy presents unique challenges, including but not limited to the rapidity of responses, the rate and depth of cytopenias, and issues related to drug–drug interactions. With the recent FDA approval and increasingly widespread use, we aim here to summarize, based on evidence and experience, emerging management strategies for the combination of HMAs and venetoclax in the treatment of AML.

Introduction

Acute myeloid leukemia (AML) most commonly affects older adults, with a median age at diagnosis of 68 [1]. Outcomes are poor for patients 60 years and older who do not receive stem cell transplantation, with only 2.4% remaining alive and disease-free 10 years after diagnosis [2]. These poor outcomes are due to patient-related factors, such as increased comorbidities [3], and disease-related factors, particularly the higher incidence of adverse-risk cytogenetic abnormalities in older AML patients [4]. Lower-intensity therapies, including the hypomethylating agents (HMA) azacitidine and decitabine, have been the mainstay of therapy for older AML patients who are poor candidates for intensive induction chemotherapy. HMA monotherapy is associated with complete remission (CR) plus CR with incomplete count recovery (CRi) rates of ~15–30%, median time to response ranging from 3 to 4 months, median overall survival (OS) of <12 months, and a generally tolerable safety profile in the older AML population [5–7].

B-cell lymphoma 2 (BCL-2) is an antiapoptotic protein that plays key roles in the survival and therapeutic resistance of AML cells, including the leukemia stem cell (LSC) population [8, 9]. BCL-2 and its family members prevent apoptosis by binding to and sequestering pro-apoptotic proteins [10]. Venetoclax is a potent, selective, oral inhibitor of BCL-2 which, in preclinical studies, demonstrated anti-AML and anti-LSC activity as a monotherapy and additive properties with azacitidine, including the ability to target LSCs through disruption of energy metabolism [8, 9, 11, 12]. In patients with relapsed and refractory (R/R) AML, venetoclax had modest single-agent activity (19% CR/CRi) [13]. In contrast, venetoclax 400 mg in combination with either azacitidine or decitabine demonstrated significant activity in the up-front treatment setting, with a CR/CRi rate of 71% and 74%, median duration of response of 21.2 and 15.0 months, and median OS of 16.9 and 16.2 months, for azacitidine and decitabine, respectively [14]. Efficacy was observed among all AML subgroups, including patients with secondary AML, those with

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adverse-risk cytogenetics, and across the genomic landscape of the disease [15]. In a separate study, venetoclax was also shown to be safe and effective in combination with low-dose cytarabine (LDAC) [16].

Based on these results, venetoclax in combination with azacitidine, decitabine, or LDAC was approved by the United States Food and Drug Administration (FDA) for use in untreated patients with AML who are 75 years or older or who have comorbidities that preclude the use of intensive induction chemotherapy [17]. Confirmatory placebo-controlled phase 3 studies with venetoclax in combination with azacitidine or LDAC are ongoing (NCT02993523 and NCT03069352, respectively).

Venetoclax plus HMA is increasingly being used in the treatment of AML, and is considered by many to now be the standard of care for this population. However, data from the clinical trials [15, 16, 18], as well as single-institution retrospective series [19, 20], have not resulted in universal consensus for the day-to-day use of this regimen. There are important nuances to its administration that have been learned through the management of a high volume of patients; these are not necessarily intuitive or relatable to other therapies, and have not been published. Here, we provide an overview of our standard practices to the administration of venetoclax plus HMA, based on evidence, as well as experience, to assist the providers who manage these patients.

On the urgency of treatment

We are typically inured to regard AML as a medical emergency, and there are times when that applies; patients with very high white blood cell (WBC) counts, those who present with end-organ damage or AML patients who are clinically unstable must be addressed swiftly. However, we have found these scenarios to be the exception, particularly in the setting of older AML patients who evolve from an antecedent hematological condition. We believe most of these patients can be addressed expeditiously but not emergently, with the luxury of some time to craft the best possible plan [21]. In the recent past, when an intensive induction chemotherapy-one-size-fits-all approach was the only viable approach to this disease, deliberation regarding the urgency of treatment was largely academic. However, in the post-venetoclax treatment era, the availability of this oral prescribed agent has made it important to again consider this issue. After we identify non-proliferative, stable outpatients, our practice is to quickly start the venetoclax acquisition process. We carefully monitor patients in the outpatient setting two to three times a week, with blood counts and transfusions according to their clinical needs or our institutional thresholds. The majority of patients can take possession of their first month's supply within 14 days of the prescription, allowing them to be scheduled for admission for venetoclax escalation and tumor lysis syndrome (TLS) monitoring and prophylaxis (see "On Monitoring for Tumor Lysis Syndrome" for our approach to dose escalation and TLS management). Alternatively, as AML practitioners know, there are instances in which treatment must be initiated urgently, for proliferative patients or those who are in extremis. In the dose escalation/expansion HMA backbone clinical trial, patients with a white blood cell (WBC) count of $> 25 \times 10^3/mm^3$ were excluded; however, hydroxyurea or leukapheresis were permitted to enroll a patient who could be cytoreduced. Historically, low-intensity therapies such as HMAs as single agents have worked poorly for patients with proliferative disease [22]. No comparison of outcomes between patients who enrolled in the venetoclax plus HMA clinical trial after requiring cytoreduction vs. those who did not has been performed, and selection bias would likely confound this analysis. However, we have found it is possible to successfully treat proliferative patients with venetoclax plus HMAs, after decreasing the pre-treatment WBC count with hydroxyurea and/or leukapheresis (our rough goal is to approximate the clinical trial and initiate therapy after achieving a WBC of $< 25 \times 10^3/mm^3$), and with intense clinical monitoring. The success of this strategy should be investigated in the setting of a prospective or retrospective study to provide further guidance. For proliferative patients, we recommend initiating treatment expeditiously, in an inpatient facility where venetoclax is available from the pharmacy "off the shelf" without prior authorization. When inpatient treatment is initiated, the appropriate requests should simultaneously be made for patients to receive the prescription as an outpatient, so they can continue therapy upon discharge from the hospital without interruption.

On monitoring for tumor lysis syndrome

TLS is a complication associated with effective treatment, caused by the release of leukemia cell contents resulting in electrolyte and metabolic abnormalities that can lead to catastrophic clinical sequelae [23]. TLS is classified either as laboratory TLS or clinical TLS, in which clinical TLS is accompanied by acute kidney injury, cardiac arrhythmias, seizures, or death [23, 24]. TLS occurs relatively infrequently in AML in the setting of induction chemotherapy (12% laboratory and 5% clinical) [25]. Because of the experience with fatal TLS events in the venetoclax study for patients with chronic lymphocytic leukemia (CLL) [26], extraordinary measures, including inpatient hospitalization and mandatory nephrology consultations, were mandated as an attempt to mitigate this outcome in AML patients. With

these precautions, there were no reports of TLS in the venetoclax plus HMA studies [15, 18], and two subjects (2.4%) had laboratory TLS in the venetoclax plus LDAC study [16]. Perhaps this was due to the aggressive mitigation techniques, or perhaps TLS was rarely seen because it is an uncommon phenomenon in AML with use of venetoclax; given data to support a novel mechanism for this therapy in AML [27], it would not be unexpected if the toxicity profile differed in this disease compared to CLL. Regardless, the severity of this toxicity, even if it is rare, in our opinion justifies the relatively benign recommendation to monitor patients initiating this therapy in the inpatient setting (Fig. 1). Perhaps in the future we will learn to risk stratify TLS monitoring in these patients, such is done with venetoclax in CLL, and only aggressively monitor those patients for whom this complication is most likely. Currently, however, we recommend admission of patients starting on venetoclax plus HMA to the hospital for TLS prophylaxis and monitoring during venetoclax dose escalation.

Specifically, our approach to TLS monitoring involves a rapid (relative to CLL) intra-patient dose escalation protocol in which venetoclax is administered as follows: 100 mg on day 1, 200 mg on day 2, and 400 mg on day 3, a dose that is continued subsequently, daily, for 28-day cycles. During dose escalation, TLS monitoring involves the collection of a complete metabolic panel, including potassium, creatinine, calcium, phosphate, uric acid and lactate dehydrogenase, every 8 h, and then every 24 h after dose escalation, for as long as the patient remains in the hospital. Allopurinol is administered 72 h prior to starting the first dose of venetoclax, and intravenous (IV) fluids are administered. Aggressive measures are taken to correct electrolyte abnormalies or hyperuricemia. The earliest patients are discharged, in the absence of any complications, is 24 h after reaching the target venetoclax dose of 400 mg (day 4), at which point they continue therapy in the outpatient setting; a daily complete metabolic panel is collected until day 7, and thereafter as clinically indicated.

On the optimal time to assess responses

Rapid responses have come to be expected in previously untreated AML patients, and this is a strength of venetoclax-based therapies. The median time to first response and best response were 1.2 months and 2.1 months, respectively, in patients treated with venetoclax plus HMA combinations [15], which compares favorably to the use of azacitidine or decitabine alone (3.2 and 4.3 months, respectively) [5, 28]. We always assess for a response after the first cycle of therapy (around day 28 of the first cycle) (Fig. 1). Owing to expectations around rapid responses, we become concerned when there is no morphologic remission after the first cycle. In this circumstance, if it is appropriate to consider continued therapy with the venetoclax-based regimen (i.e., significant blast reduction was achieved compared to baseline), we would check a bone marrow biopsy after the second cycle. In the absence of a morphologic remission after cycle 2 we would be pessimistic that continued therapy would be effective and typically recommend other treatment options (which is notably distinct from the typical approach to a non-responder after two cycles with a single-agent HMA). In the setting of a positive response after the first or second cycles, we routinely check bone marrow biopsies after cycle 4 and then every six months thereafter, in the absence of clinical suspicion for disease relapse (Fig. 1).

On the management of venetoclax-associated cytopenias

Of all of the issues related to the administration of venetoclax, the most frequent concern, in our opinion, relates to the associated cytopenias and best practices to manage them.

Primarily, one important consideration with respect to cytopenias is to ascertain whether they are clinically significant. Patients with cytopenias who are symptomatic, require transfusion support, or have infectious complications should be managed differently than patients who have cytopenias that have no clear clinical sequalae. Anecdotally, we have many patients receiving venetoclax-based regimens who are cytopenic but have a very good quality of life and have been in long-term remissions with no clinical consequences from their "low" blood counts. Some of these patients, frequently those who evolved from an antecedent myelodysplastic syndrome (MDS), even show evidence of a reversion to the prior low-grade MDS state, with the expected accompaniment of cytopenias. Comparing the adverse events of patients who received venetoclax 400 mg plus azacitidine with patients from a phase 3 study who received azacitidine alone [6], there appears to be an increased degree of myelosuppression from the addition of venetoclax, but it is unclear if this results in worsened clinical consequences (Table 1). There are many obvious limitations in attempting to compare the results of two unrelated clinical trials, and ultimately the randomized phase 3 studies in progress (NCT02993523 and NCT03069352) will help to clarify the additional toxicity from venetoclax compared to azacitidine and low-dose cytarabine (LDAC). If adverse events from cytopenias, and not just cytopenias themselves, do not significantly differ between the two arms, a

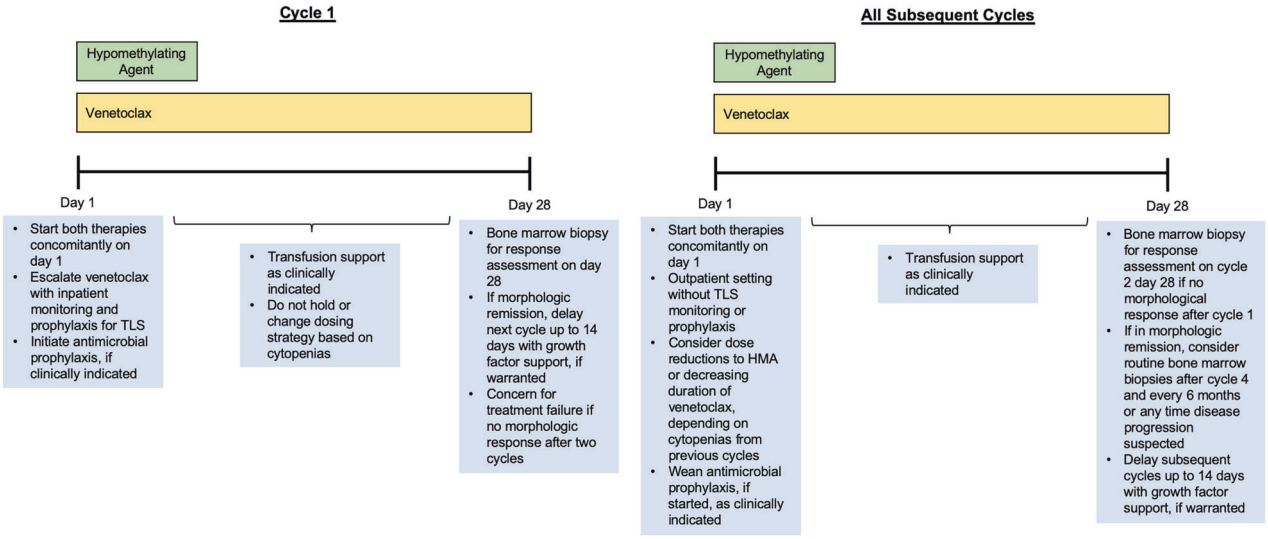

Fig. 1 Venetoclax plus hypomethylating agent treatment schema for cycle 1 (left panel) and subsequent cycles (right panel). Key management points are summarized below each panel. TLS tumor lysis syndrome; HMA hypomethylating agent

Table 1 Comparison of the most frequent grade 3 to 4 treatment-emergent adverse events from two separate studies of newly diagnosed acute myeloid leukemia patients treated with venetoclax plus azacitidine vs. azacitidine alone

Treatment-emergent adverse events	Venetoclax 400 mg + azacitidine ($N = 84$) [14]	Azacitidine ($N = 236$) [6]
Leukopenia	33%	7%
Febrile neutropenia	39%	28%
Pneumonia	27%	20%
Thromboctyopenia	26%	24%
Anemia	31%	16%

strong case could be made to encourage practitioners to tolerate low blood counts, particularly in the absence of clear clinical sequalae.

We have found that for the majority of patients, cytopenias can be successfully managed. Primarily, until a response is assessed, we strongly advocate continuing this regimen with aggressive supportive care and discourage treatment interruption or dose reductions in either therapy (Fig. 1). Those who regularly treat AML are accustomed to the principle that initial therapy, whether it is intensive or less intensive, mandates this approach. This should extend even more so to venetoclax-based regimens, with their high-response rates, rapid remissions and low early-death rates (3%), which translates to a lower risk: benefit ratio than conventional therapies [15].

As previously stated, we recommend a response assessment with a bone marrow biopsy after the first cycle (around day 28). When evidence for at least a morphologic remission exists, in the absence of count recovery, a pause before the next cycle is warranted. We routinely allow up to a 14-day break from both therapies between cycles in this setting, and we find that growth factor support can rapidly correct neutropenia in many cases (Fig. 1). Specifically, we administer a dose of granulocyte-colony stimulating factor (G-CSF) every two to 3 days, with a goal of an absolute neutrophil count (ANC) greater than $1 \times 10^3/mm^3$ during that 14-day period off therapy. We do not administer G-CSF if there is morphologic evidence of residual disease and never give it in the middle of the initial treatment cycle (days 1–28) or less than 7 days before a planned bone marrow biopsy.

Regarding formal assessments of response, we believe the "up-graded" response, from a morphologic leukemia free state (MLFS) to a CR/CRi or a CRi to a CR, is appropriate to report assuming it has occurred within 14 days of the bone marrow biopsy and no intervening disease modifying therapy has been administered [29]. Some patients do not have significant cytopenias and achieve a full CR/CRi after the first cycle; even in these situations we routinely delay the next cycle, especially because the bone marrow results can take several days and patients typically appreciate a treatment-free interval. In situations in which there has been blast reduction but residual disease is obvious, and it is felt more therapy may be beneficial, we advocate starting the subsequent cycle of therapy without delay, and withholding the use of growth factor support. A post-cycle 2 bone marrow biopsy should be performed in these cases to properly assess response. In responders after the first or second cycles, we repeat a bone marrow biopsy for disease assessment after cycle 4 and

continue to assess response every six cycles or as clinically indicated (Fig. 1).

Continuing to incorporate breaks between cycles for patients with cytopenias is recommended (Fig. 1). Sometimes the blood counts fully recover; in these instances, breaks between cycles are optional and can be given based on patient preferences. When cytopenias continue, or are worsening, breaks as outlined above, with or without growth factor support, should be mandatory. Dose reductions can also be of use for patients with cytopenias. Venetoclax can be reduced to 21 days with each treatment cycle, but no data exists regarding how this impacts the efficacy of the regimen. Anecdotally we have several patients in long-term remission who continue on these truncated schedules. We do not recommend decreasing the actual dose of venetoclax (unless it is necessary for drug–drug interactions), but instead we decrease the duration of venetoclax treatment with each cycle; no evidence supports this preference. The role of antimicrobial prophylaxis and venetoclax dose reductions for drug–drug interactions are discussed further elsewhere in this paper (see "On Antifungal Prophylaxis and Treatment"). Azacitidine or decitabine can also be dose reduced; we typically follow the package insert to guide azacitidine dose changes and institutional practice guidelines inspired by the literature to adjust decitabine [30], and we have seen improvements in cytopenias with these strategies.

Some patients in remission with cytopenias have discontinued the HMA; it is unclear how this might impact the response duration. In a previously reported data set of 33 patients treated with azacitidine and venetoclax, 19 ultimately stopped azacitidine for cytopenias (four stopped all therapy) [27]. Of these patients, ten have not or did not relapse (with median follow up time of 865 days) and nine relapsed, with a median response duration of 232 days (168–930) (unpublished data). Clearly more information is needed on whether this strategy can be effective; there is a clinical trial investigating whether decisions about the duration of azacitidine can be informed by measurable residual disease (MRD) testing (NCT03466294). Finally, we have seen some patients who relapse after discontinuing the azacitidine re-respond when the azacitidine is added back, but these responses have not been durable. Overall and based on current data, we recommend continuing the venetoclax plus HMA combination therapy indefinitely, with incorporation of dose reduction and/or delay strategies to mitigate the risk of adverse events.

On antifungal prophylaxis and treatment

Neutropenia is a common occurrence in patients with AML and leads to infectious complications such as febrile neutropenia, sepsis, and bacterial, viral, and fungal infections. As a result, antimicrobial prophylaxis, frequently with an antibacterial, antiviral, and antifungal therapy, is widely used [31, 32]. Much of the data to support this comes from two large randomized studies in patients that showed reduced rates of infections and related complications with levofloxacin compared with placebo and posaconazole compared to other antifungal therapies [33, 34]. However, antimicrobial prophylaxis remains controversial and is not universally adopted [35].

Owing to drug–drug interactions with "azole" antifungals, which are moderate to strong CYP3A4 inhibitors, and venetoclax, these therapies were not permitted in most patients who participated in the venetoclax plus HMA clinical trials [15, 18]. A small drug–drug interaction sub-study within the trial did provide guidance for a recommended dose reduction of venetoclax in the presence of azoles [36]; unfortunately, apart from a similar response rate seen in this small patient subset, no data have been reported as to whether other outcomes of these patients were consistent with patients who were not dose reduced [18], raising theoretical concerns that dose reductions may impair efficacy.

In a retrospective analysis of patients with AML and MDS treated with HMAs without antifungal prophylaxis, the rate of invasive fungal infections was 4.1% [37]. In patients treated with venetoclax plus HMA without azole prophylaxis, the rate of grade 3/4 fungal infections was 8%; however, 46% of patients received non-azole antifungal (e.g., echinocandin) prophylaxis [15].

We are currently in a transition period, between having access to venetoclax but not fully understanding the implications of dose reductions, which makes it difficult to proceed with any one strategy related to antifungal prophylaxis with confidence. We believe that given the fact that a) antifungal prophylaxis is not a universal recommendation for AML patients undergoing treatment, and b) the clinical efficacy of the reduced doses of venetoclax when given with azoles is uncertain, antifungal prophylaxis with venetoclax plus HMAs need not be mandatory. However, we acknowledge that this goes against the typical practice of many providers influenced by patient, environmental and institutional factors, and it is possible that the relatively low rate of fungal infections seen in the venetoclax plus HMA trial was related to echinocandin use. Therefore, we also cannot recommend against the routine use of antifungal prophylaxis, although the optimal choice of antifungal agent is not known. It may be possible to provide antifungal prophylaxis, without venetoclax dose reductions, by using echinocandins, which have demonstrated activity in the prophylactic setting, have anti-aspergillus activity, and can be dosed intermittently [38–42]. However, if azole antifungals are given as prophylaxis we suggest abstaining from them during the dose escalation period of cycle 1, and

waiting to administer them, with the appropriate decrease in venetoclax dose, after the target dose has been achieved so as not to change the risks for or recognition of TLS. Regarding antiviral and antibacterial prophylaxis, we also acknowledge that there is widely variable institutional and personal practices and there is insufficient evidence reported from the venetoclax plus HMA clinical trial to mandate this [43]. Unlike azoles, most commonly used antiviral and antibacterial prophylactic agents do not require venetoclax dose adjustments. There is also no data to guide the duration of antimicrobial prophylaxis in patients receiving venetoclax plus HMA therapy. Generally, in our practice we wean antimicrobial prophylaxis in responders with less frequent and shorter periods of severe neutropenia (Fig. 1).

Antifungal treatment is different from prophylaxis, and when AML patients, especially those who are neutropenic, have confirmed or suspected fungal infections, aggressive therapy is not optional. Echinocandins can be effective antifungal therapies, and as mentioned above do not require venetoclax dose reductions. However, their efficacy may not be adequate and delivery mechanisms and costs can be limiting. Therefore, in the appropriate setting we do not hesitate to use azole antifungals. For strong CYP3A4 inhibitors the recommended venetoclax dose reduction from 400 mg is 70 mg for posaconazole and 100 mg for other strong inhibitors (e.g., voriconazole); we typically reduce to 100 mg for all strong inhibitors due to challenges acquiring 70 mg venetoclax tablets for AML patients. We have little concern for effective venetoclax doses greater than 400 mg due to the safety profile demonstrated up to a dose of 1200 mg of venetoclax in the phase 1 studies [18]. For the moderate CYP3A4 inhibitor isavucaonzole, we decrease the venetoclax dose to 200 mg, and therefore prefer it if it can be obtained, including in the prophylactic setting. Additional studies evaluating the use and efficacy of specific antimicrobial prophylaxis agents in patients treated with venetoclax plus HMA are necessary for clarity on this issue.

On the consideration of genomically defined targeted therapies in the venetoclax era

In the AML field, we are fortunate to provide care to patients in an era in which the molecular understanding of this disease arguably exceeds that of any other human malignancy. The rich understanding of the genomic makeup of each patients' disease has logically led to genomically defined targeted therapies that are FDA approved and accessible. This applies to *isocitrate dehydrogenase* (*IDH)* and *Fms-like tyrosine kinase 3* (*FLT3)*, common AML mutations for which there are four FDA-approved drugs for three distinct patient populations. Inevitably, patients for whom we prescribe venetoclax-based regimens have these mutations, and we must determine whether to use venetoclax-based regimens, genomically targeted therapies, or perhaps, a combination of the two strategies.

Practically, the only other targeted therapy that is FDA approved for an untreated, newly diagnosed AML patient deemed unfit for intensive chemotherapy is the *IDH1* inhibitor ivosidenib [44]; there is no labeled indication for single-agent enasidenib in the up-front treatment setting. We incorporate *IDH1* into our next generation sequencing (NGS) panels, but these take 2 to 3 weeks to provide results; there are platforms that would allow this information to be acquired in a faster, more clinically actionable timeframe, but we decline to employ these, because we do not feel this information is necessary before initiating treatment with venetoclax-based therapies in the newly diagnosed AML setting. In combination with HMA, venetoclax has high-response rates in all molecular subtypes of AML [15, 18]. *IDH1/2*-mutated patients have shown particularly high-response rates in all clinical trials of venetoclax in AML [13, 15, 18]; 25 patients with an *IDH1/2* mutation treated with venetoclax 400 mg and a HMA had a 92% CR/CRi rate with an OS not reached [14]. Although numbers are small and there are obvious limitations in attempting to compare independent clinical trials, 33 newly diagnosed AML patients with an *IDH1* mutation treated with ivosidenib had a 42% CR/CR with partial recovery of blood counts (CRh) and a median OS of 12.6 months [45]. Similarly, 39 newly diagnosed AML patients with an *IDH2* mutation treated with single-agent enasidenib had a 21% CR/CRi rate and median OS of 11.3 months [46]. The same applies for patients with a *FLT3* mutation, and when one analyzes the very small numbers of newly diagnosed patients with a *FLT3* mutation treated with azacitidine and the *FLT3* inhibitor sorafenib, the response rate was 50% (3/6) [47], compared with 64% (9/14) for patients treated with venetoclax and a hypomethylating agent (HMA) [14]. These comparisons are summarized in Table 2. Therefore, an additional advantage of the use of venetoclax in the up-front setting is that it appears to allow some degree of confidence that optimal outcomes can be had regardless of mutational profiles, preserving opportunities to target *FLT3* or *IDH* in the relapsed setting. Studies combining other targeted therapies with venetoclax-based treatments in the up-front setting are ongoing (e.g., NCT03471260); we do not recommend these approaches outside of a clinical trial and eagerly await these results.

On expected outcomes in previously treated AML patients

In contrast to the high response rates and encouraging durability of responses and OS in the front-line setting with

Table 2 Comparison of key clinical results of newly diagnosed acute myeloid leukemia patients with *IDH* or *FLT3* mutations treated venetoclax plus hypomethylating agents vs. specific inhibitors of *IDH* or *FLT3*

Isocitrate dehydrogenase			
	Enasidenib ($N = 39$)	Ivosidenib ($N = 33$)	Venetoclax 400 mg + Hypomethylating Agent ($N = 25$)
Response rate	21% CR/CRi	42% CR/CRh	92% CR/CRi
Time to best response (months)	3.7	2.8	Not available (2.1 for the entire study population)
Duration of response	Not Reached	Not Reached	Not available (11.3 months for the entire study population)
Median event-free survival (months)	5.7	Not available	Not available
Median overall survival (months)	11.3	12.6	Not available (17.5 months for the entire study population)
Citation	Pollyea et al., Leukemia [29]	Roboz et al., ASCO [45]	Pollyea et al., ASH [14, 27]; Dinardo et al., Blood [15]

FLT3		
	Sorafenib + Azacitidine ($N = 6$)	Venetoclax 400 mg + Hypomethylating agent ($N = 14$)
Response rate	50% (CR/CRi)	64% (CR/CRi)
Time to best response (months)	Not available	Not available (2.1 for the entire study population)
Duration of Response	Not available	Not available (11.3 months for the entire study population)
Median overall survival (months)	Not available	Not available (17.5 months for the entire study population)
Citation	Ravandi et al., Blood [47]	Pollyea et al., ASH [14, 27]; Dinardo et al., Blood [15]

IDH isocitrate dehydrogenase, *FLT3* fms-like tyrosine kinase 3, *CR* complete remission, *CRi* complete remission with incomplete recovery of peripheral blood counts, *CRh* complete remission with partial hematologic recovery

venetoclax-based combinations, the efficacy of venetoclax monotherapy and combinations in the relapsed or refractory (R/R) AML setting is more modest. As a single-agent, venetoclax showed a 19% CR/CRi rate in a cohort of predominately R/R AML patients [13]. Responses were brief, with a median time to progression of 2.5 months and a median OS of 4.7 months. There is also data for venetoclax combinations in the R/R setting from retrospective single-institution experiences. In one such study, 43 R/R patients, including 84% in the second or higher salvage setting, were treated with venetoclax-based combinations ($N = 23$ decitabine, 8 azacitidine) [19]. In this population, 12% achieved a CR/CRi and the median OS was three months. Another study examined 33 R/R patients who received venetoclax with a HMA ($N = 31$ decitabine, 2 azacitidine) [20], and showed 51% achieved CR/CRi with 12-month OS of 53% and 14% proceeding to allogeneic stem cell transplantation.

Therefore, when venetoclax or venetoclax-based regimens are used in the R/R setting, appropriate expectations are necessary. Interestingly, in the R/R setting responses typically still occurred rapidly, within 1–2 cycles of therapy [19, 20]. More data is needed to understand outcomes from patients treated with this salvage approach who proceed to transplantation, as well as the role for novel venetoclax combinations in the R/R population. In the meantime, when venetoclax is obtained and used off-label for R/R patients, caution should be employed, and it must be acknowledged that the dose and schedule, TLS management, toxicities, and recommendations related to disease assessments are not yet clear. Enrollment into appropriate clinical trials is essential for the field.

Historically, patients with AML with myelodysplasia-related changes or secondary AML have had poor outcomes [48–50]. In contrast, in the venetoclax plus HMA clinical trial, there were not major differences in outcomes for de novo vs. secondary AML with respect to response rates [15]. However, patients with MDS who receive a HMA and then progress to AML are treatment naive with respect to their AML, but may behave like R/R patients when it comes to response to venetoclax-based regimens. The venetoclax plus LDAC study for newly diagnosed AML patients demonstrated a CR/CRi rate of 54%, compared to around 70% for patients who received venetoclax with a HMA backbone therapy [15, 16]. One possible explanation for this difference was that the LDAC study enrolled patients who had been exposed to HMAs for MDS, while the HMA backbone study excluded these patients. In the LDAC study, 29% of patients had prior HMA exposure, and their response rate was only 33%; when accounting for this sub-group, the response rates of the truly treatment-naive LDAC patients is commensurate with the HMA backbone therapy patients (62% CR/CRi) [16]. Furthermore, a recent analysis of patients who received off-label venetoclax showed prior HMA exposure to be a significant predictor of a worse outcome (Winters et al., Blood Advances, Publication Pending). In cases such as the one above, there is still a reasonable enough chance of a response that venetoclax can be added when progression to AML occurs. However, in this setting, appropriate expectations are necessary. A study to determine responses when venetoclax is added to a HMA for MDS patients who do not respond or lose their response to this therapy (but do not progress to AML) is ongoing (NCT02966782).

In newly diagnosed AML patients with no prior exposure to a HMA, practitioners may be tempted to start the HMA and add in the venetoclax either whenever it is able to be obtained or when it becomes obvious that the HMA is not effective. We strongly discourage this practice, as we believe, extrapolating from the above data, that this strategy has the potential to undermine the response of the combined regimen. Until more is known, safely delaying the start of therapy until both treatments can be administered simultaneously on day 1 should be prioritized (Fig. 1).

On the optimal backbone therapy with venetoclax

Venetoclax is approved to be administered with azacitidine, decitabine, or LDAC. Our preference is to use azacitidine, due to data showing that azacitidine with venetoclax can target the leukemia stem cell population [27]; while this may be possible with decitabine or LDAC, it has not been shown. In addition, azacitidine is the backbone therapy of choice in the ongoing confirmatory phase 3 study (NCT02993523), and is being used for the above-mentioned ongoing MDS HMA failure study (NCT02966782). However, there is no clear evidence for superiority of a particular venetoclax partner among the three approved combination agents. In the scenario in which a patient had prior exposure to one HMA for MDS and then progresses to AML, it would not be unreasonable to alter the backbone treatment in the hopes that introducing two new therapies may allow for the best possible chance of response. In fact, as stated above, this situation was approximated in nearly one-third of patients enrolled in the LDAC-backbone study, so the use of this combination in this setting would arguably allow for the most predictable outcomes. Owing to published data showing decitabine may be more effective as a single-agent in patients with complex karyotypes and/or mutations in *TP53* [51], some may prioritize the use of decitabine in these situations, and this would be a reasonable approach. Other decisions regarding choice of a backbone therapy may be based on factors such as patient preference (e.g., 5, 7, or 10-day chemotherapy schedules) or logistical issues (e.g., weekend infusion hours, ability to procure and prescribe LDAC).

Conclusions

Venetoclax plus HMA results in a broad response rate across AML subgroups, allows for deep and durable responses with promising OS, and is a well-tolerated regimen for older, newly diagnosed AML patients. While it is less complicated than many of the multi-agent chemotherapy regimens blood cancer providers are accustomed to giving, venetoclax plus HMA is a new therapy, and limited experience, as well as assumptions based on experience with HMA alone, can limit the efficacy of this treatment. There are many important nuances of this regimen that require special attention from the community treating these patients. As we gain more experience with this regimen, there are many active questions that remain. In the near future, we look forward to a similar review that will describe: (1) which patients may not require conservative TLS mitigation strategies; (2) which responding patients may be able to abandon one or possibly both therapies; and (3) who might be predicted to have a poor response to this therapy and should be treated with another regimen. Venetoclax plus HMA is a promising treatment for AML patients that we believe will serve as a therapeutic pillar for this disease in the years to come.

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Author contributions BAJ and DAP developed the concept and wrote and edited the manuscript. Both authors approved the final version.

Compliance with ethical standards

Conflict of interest Dr. Jonas has served in a consulting/advisory role for AbbVie, Amgen, Celgene, GlycoMimetics, Jazz, Pharmacyclics, and Tolero. He has received travel support from AbbVie, Amgen, and GlycoMimetics. He has received research funding to his institution from AbbVie, Accelerated Medical Diagnostics, AROG, Celgene, Daiichi Sankyo, Esanex, Forma, Genentech/Roche, GlycoMimetics, Incyte, KaloBios, LP Therapeutics, and Pharmacyclics. Dr. Pollyea has received research funding from Abbvie and Pfizer. He has served in a consulting/advisory role for Pfizer, Abbvie, Diachii Sankyo, Celgene, Agios, Janssen, 47, and Takeda.

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