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Hypomethylating agents in the treatment of acute myeloid leukemia: A guide to optimal use

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ABSTRACT

The hypomethylating agents (HMAs), decitabine and azacitidine, are valuable treatment options in acute myeloid leukemia patients who are not eligible for intensive chemotherapy. Both agents are generally well tolerated, and complications most commonly relate to myelosuppression. Antibiotic / antifungal use, regular monitoring, and proactive patient education are important to minimize these events, and reduce the need for dose delay. Responses to HMAs are often not evident for up to 6 cycles, and there is currently no validated clinical marker for predicting response. Hence, treatment should be continued for at least 4–6 cycles to ensure that patients have sufficient opportunity to respond. Delivery of insufficient numbers of cycles is a key reason for HMA failure, and premature discontinuation must be avoided. Genetic factors offer potential for better predicting responders to HMAs in future, but require further study.

1. Introduction

Hypomethylating agents (HMAs) are an important treatment option in patients with acute myeloid leukemia (AML) who are not considered to be candidates for intensive chemotherapy (Döhner et al., 2017). Two HMAs have been licensed in Europe for the treatment of these patients: decitabine and azacitidine (Dacogen SmPC; Vidaza SmPC). Both are indicated for the treatment of adult patients with newly diagnosed AML who are not candidates for standard induction chemotherapy (Dacogen SmPC; Vidaza SmPC). Both work by DNA methyltransferase-1 depletion, DNA hypomethylation, and chromatin reorganization (Hollenbach et al., 2010; Kim et al., 2015). Azacitidine has effects on both RNA and DNA, whereas decitabine has no direct effects on RNA (Kim et al., 2015)

The use of HMAs in AML follows the experience with these drugs in myelodysplastic syndrome (MDS), and there is significant overlap in the recommendations for practical use. However, it is important to remember that AML patients have distinctive clinical characteristics.

Decitabine and azacitidine have proven efficacy and safety in Phase 3 trials in AML. The DACO-016 study randomized 485 patients aged ≥ 65 years (who were not considered to be candidates for standard induction chemotherapy) to either decitabine 20 mg/m^2/day as a 1 -h intravenous (IV) infusion for 5 consecutive days every 4 weeks or to treatment choice (TC; best supportive care [BSC] or cytarabine 20 mg/m^2/day as a subcutaneous [SC] injection for 10 consecutive days every 4 weeks) (Kantarjian et al., 2012). The primary analysis showed a non-significant increase in median overall survival (OS) with decitabine versus TC (7.7 vs 5.0 months, respectively; hazard ratio [HR]: 0.85; 95% confidence interval [CI]: 0.69–1.04; p = 0.108); this difference became statistically significant in a pre-planned analysis in which patients who received subsequent disease-modifying therapy were censored (median OS: 8.5 vs 5.3 months; HR: 0.80; 95% CI: 0.64–0.99; p = 0.044), and in an unplanned mature analysis (median OS: 7.7 vs 5.0 months; HR: 0.82; 95% CI: 0.68–0.99; p = 0.037) (Kantarjian et al., 2012). Meanwhile, the AZA-AML-001 trial randomized 488 patients aged ≥ 65 years to azacitidine 75 mg/m^2/day SC for 7 consecutive days every 4 weeks or conventional care (BSC, cytarabine 20 mg twice daily for 10 consecutive days every 4 weeks, or induction chemotherapy with cytarabine and daunorubicin/idarubicin) (Dombret et al., 2015). There was a non-significant improvement in median OS with azacitidine versus conventional care (10.4 vs 6.5 months, respectively; HR: 0.85; 95% CI: 0.69–1.03; p = 0.101), which reached statistical significance when censoring patients who received AML treatment after discontinuing study drug (median OS: 12.1 vs 6.9 months; HR: 0.76; 95% CI: 0.60–0.96; p = 0.019) (Dombret et al., 2015).

No randomized trial has ever directly compared decitabine and azacitidine in AML. Furthermore, indirect comparisons of the Phase 3 trials are complicated by important differences in the inclusion criteria,

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comparator arm, and treatment duration (Kantarjian et al., 2012; Dombret et al., 2015; Schuh et al., 2017). A recent analysis of outcomes from > 2000 patients receiving frontline AML treatment with decitabine or azacitidine in a US database found that median OS was similar with the two compounds (Mehra et al., 2017). Similarly, retrospective analyses in patients with MDS have typically found no difference between decitabine and azacitidine in OS or response rates (Lee et al., 2013a; Zeidan et al., 2016), although a Korean study observed that each HMA may be superior to the other in particular patient subgroups (Lee et al., 2013b). Current AML guidelines from the European LeukemiaNet (ELN) give both drugs equal weighting as options for patients who are not candidates for intensive chemotherapy (Döhner et al., 2017).

There is currently no widely adopted, standardized definition of 'suitability' or 'fitness' for intensive chemotherapy. However, attempts have been made to establish such a classification. For example, the Italian hematology and transplant societies developed a definition based on factors such as age, comorbidities and performance status (Ferrara et al., 2013). Furthermore, the use of extended geriatric assessments focusing on cognitive and physical function may improve the prediction of survival in older patients being considered for induction chemotherapy (Klepin et al., 2013; Sherman et al., 2013; Klepin, 2014). Given that it is often their only chance for cure, all patients should be assessed for intensive treatment but, in practice, many patients are considered not to be fit enough to receive it.

2. Administration of HMAs

The recommended dose and administration of both approved HMAs is as per the Phase 3 registration trials. Decitabine should be given at 20 mg/m^2 of body surface area, IV, daily on the first 5 days of each 4-week cycle (Dacogen SmPC). A central venous catheter is usually not required. Decitabine infusion should last 1 h. For azacitidine, the recommended schedule is 75 mg/m^2 of body surface area, SC, given daily on the first 7 days of each 4-week cycle (Vidaza SmPC). For both drugs, a protocol of administration should be developed by individual centers, providing also hydration and anti-emetics, if required. In the majority of patients, HMAs can be given on an outpatient basis; home administration could be a possibility with azacitidine although this is currently not allowed in many countries. Subcutaneous injections can be given in the abdomen, legs or arms in a clockwise fashion, without exceeding 1 mL infusion per injection site and without priming the syringe.

Either HMA should be continued for a minimum of 4–6 cycles unless clear progression or intolerance are documented (Dacogen SmPC; Vidaza SmPC).

Other HMA dosing regimens have been assessed. In fact, decitabine was first studied with a different schedule and dose – 15 mg/m^2 decitabine given three times daily on 3 consecutive days (total dose 135 mg/m^2) every 6 weeks – based on its pharmacokinetics and supposed hypomethylating activity, and the safety and efficacy of this regimen has been demonstrated (Lübbert et al., 2012). Furthermore, a decitabine schedule of 20 mg/m^2/day given for 10 days of each 28-day cycle has shown promising results across several studies (Blum et al., 2010; Ritchie et al., 2013; Bhatnagar et al., 2014; Welch et al., 2016), and a meta-analysis of non-comparative studies suggested that response rates were significantly higher than with the conventional 5-day regimen (He et al., 2017a). However, a recent, randomized Phase 2 study comparing the efficacy of the 5- and 10-day regimens in adults aged ≥ 60 years with newly diagnosed AML found no significant difference in response rate or survival (Short et al., 2017). An ongoing Phase 3 study run by the European Organisation for Research and Treatment of Cancer (EORTC) is comparing 10-day decitabine with standard '7 + 3' combination chemotherapy followed by allografting in patients aged ≥ 60 years with newly diagnosed AML (NCT02172872).

With azacitidine, practical considerations based around avoiding weekend administration have led to the use of alternative regimens, such as 5 days of azacitidine 75 mg/m^2/day, or 5 days followed by a weekend break followed by an additional 2 days of azacitidine 75 mg/m^2/day. There has been no signal to intimate that this results in inferior outcomes, but no studies have yet made a direct comparison and these regimens have not been approved. A systematic review of studies conducted in patients with AML, MDS or chronic myelomonocytic leukemia suggested similar response rates across dosing schedules (Shapiro et al., 2015).

A recent Phase 2 study in 113 patients with lower-risk MDS or MDS/myeloproliferative neoplasm demonstrated the efficacy and safety of a shortened 3-day schedule of decitabine 20 mg/m^2/day or azacitidine 75 mg/m^2/day (Jabbour et al., 2017). Overall response rates with low-dose decitabine or azacitidine were 70% and 49%, respectively ($p = 0.03$), and 6-week mortality was 0%. However, neither 3-day schedule has been tested in AML.

For the moment, in the context of normal clinical practice, physicians should adhere to conventional HMA regimens as per their approved indications, based on their proven response rates and effects on survival (Dacogen SmPC; Vidaza SmPC).

3. Managing adverse events

Both HMAs were generally well tolerated in Phase 3 trials in AML, and rates of discontinuation due to treatment-related adverse events (AEs) were low (< 10%) given the context of higher-risk older patients (Kantarjian et al., 2012; Dombret et al., 2015).

3.1. Hematologic AEs

Although decitabine and azacitidine are less cytotoxic than intensive chemotherapy and are very rarely associated with AEs like mucositis or hepatic damage, specific considerations remain when managing this population, who are frequently elderly and/or comorbid. Indeed, AML outpatients always require particular care and attention, especially during the intervals between cycles when they are managed at home. AEs with azacitidine or decitabine are most commonly related to myelosuppression or the complications of myelosuppression (e.g. infection or bleeding) (Kantarjian et al., 2012; Dombret et al., 2015). Prophylactic wide-spectrum antibiotic use is recommended in patients receiving HMA therapy, and prophylactic antifungal use should also be considered if the neutrophil count falls below 500/μL.

Growth factor support has no proven benefit in AML, but can be employed in the intervals between cycles in case of infection and persistent severe neutropenia. However, these compounds are not recommended during the days in which HMAs are administered, owing to the S-phase specificity of the drugs and the growth factor-induced stimulation of hematopoietic cell proliferation. Concurrent administration of myeloid growth factors and an HMA may result in higher uptake of the drug and an increase in cytotoxicity, although this has not been specifically demonstrated in clinical trials.

Complete blood and platelet counts should be taken before each treatment cycle, and on a weekly basis during the treatment itself (particularly during early cycles) (Dacogen SmPC; Vidaza SmPC). Patients should be monitored for myelosuppression, as well as signs of infection or bleeding, and treated promptly. Patients with AML receiving HMA treatment normally need not be hospitalized, given the typically long duration of therapy (at least 6 cycles). Hence, they must be followed with particular attention, with at least weekly counts, and instructed to contact the treating physician immediately if they experience a fever or any persistent symptom like dyspnea, cough or bleeding. Transfusions should be performed as required and possibly programmed, particularly during early cycles in cases of symptomatic anemia or thrombocytopenia.

If a patient experiences myelosuppression-associated complications, the best strategy is not to lower the dose, but to delay the next treatment cycle at the discretion of the treating physician. In clinical trials, around a third of patients required at least one such delay (Dacogen

SmPC), although the proportion is lower in our practice, probably through more optimal application of antibiotic and antifungal agents. The decitabine Summary of Product Characteristics (SmPC) lists the following as potential situations in which dose delay might be considered (Dacogen SmPC), and the same broadly applies with azacitidine:

- Febrile neutropenia (temperature ≥ 38.5 °C and absolute neutrophil count < 1000/μL);
- Active viral, bacterial or fungal infection (requiring IV anti-infectives or extensive supportive care);
- Uncontrollable hemorrhage (gastrointestinal, genitourinary, pulmonary, or any central nervous system hemorrhage).

Treatment should be resumed as soon as possible once the patient's condition has been stabilized or improved. Cycles should not be delayed longer than necessary, owing to the presumed mechanism of action of hypomethylating agents: if the interval is excessive, DNA hypermethylation may be restored and the efficacy of treatment diminished.

In decitabine-treated patients, dose reduction is not recommended as an alternative to dose delay in cases of myelosuppression (Dacogen SmPC). The same approach is preferred with azacitidine, although the Summary of Product Characteristics (SmPC) recommends a dose reduction of 50% if a recovery in absolute neutrophil / platelet counts is not achieved within 14 days (Vidaza SmPC). It should be stressed that, in practice, this is rarely applicable, because neutrophil counts are often very low at the start of therapy.

If hematologic values do not return to pre-treatment levels or improve within 4 cycles, it may be necessary to re-evaluate a marrow aspiration to assess disease progression, and terminate HMA therapy and consider other options.

In our experience, the same dose and schedule should be maintained throughout the early cycles of therapy, whenever possible, to increase the likelihood of achieving a response.

3.2. Non-hematologic AEs

With either HMA, patients may occasionally experience an increase in body temperature during the days of administration. Other key non-hematologic AEs are described below.

3.2.1. Gastrointestinal AEs

Gastrointestinal AEs are common with HMAs, and may include nausea, vomiting, diarrhea and constipation. In Phase 3 trials, most of these were graded mild or moderate, and severe events were relatively rare (Dombret et al., 2015; Nieto et al., 2016). Pre-medication for the prevention of nausea and vomiting should be considered (Vidaza SmPC), and then re-evaluated throughout treatment, taking into account the patient's individual symptoms. In general, these events are easily managed symptomatically using anti-emetics for nausea and vomiting (before administering the drugs), anti-diarrheals for diarrhea, and laxatives or stool softeners for constipation. Constipation often relates to the use of anti-emetics and resolves in the intervals between cycles.

It is recommended to discuss all of these possible AEs with the patient before starting treatment so that they can be prevented with appropriate diet or self-medication.

3.2.2. Local AEs

Injection-site reactions are common with subcutaneously administered azacitidine, although these events were not associated with any discontinuations in the AZA-AML-001 study (Dombret et al., 2015). Injection sites should be rotated, and cases of rash, inflammation, pruritus or erythema can be managed with antihistamines, corticosteroids, evening primrose oil (Platzbecker et al., 2010), or non-steroidal anti-inflammatory drugs. Some patients have more severe skin reactions, and hemorrhagic reactions can occur, particularly when patients are severely thrombocytopenic.

There are no reports of local AEs with decitabine, even in cases of accidental extravasation. Unless venous access is particularly difficult, the use of a central venous catheter is not required.

4. Use of concomitant medications

Hydroxyurea is frequently used in AML patients to reduce white blood cell counts. However, when used in combination with decitabine or azacitidine in cell lines, hydroxyurea antagonized DNA methylation inhibition (Choi et al., 2006). Hence, it should not be used concomitantly with HMA therapy. However, this effect can be avoided through sequential use (Choi et al., 2006), and hydroxyurea may be used, if required, before initiating HMA treatment.

No formal clinical drug interaction studies have been conducted with either decitabine or azacitidine (Dacogen SmPC; Vidaza SmPC). However, neither appears to be metabolized via cytochrome P450 isoenzymes and interactions relating to these enzymes are considered to be unlikely.

5. Special populations

No formal studies have been conducted with decitabine or azacitidine in patients with hepatic impairment (Dacogen SmPC; Vidaza SmPC). Patients should be monitored closely, but no specific modifications to the dose or frequency of administration are recommended.

In a study of patients with various tumor types who had renal impairment, azacitidine pharmacokinetics were unaffected (Laille et al., 2014). The SmPCs for both approved HMAs state that these drugs can be used in patients with renal impairment, and no specific modifications to the dose or frequency of administration are recommended (Dacogen SmPC; Vidaza SmPC). However, caution should be exercised and close monitoring may be necessary, particularly in patients with severe renal impairment. Indeed, a study of 41 HMA-treated patients with renal insufficiency (n = 17 AML) suggested a higher incidence of toxicity in these individuals (Batty et al., 2010). No trials have been performed in dialysis patients, although case studies in higher-risk MDS have demonstrated successful use of azacitidine (Ham et al., 2012; Yoshihiro et al., 2016).

A recent retrospective evaluation noted a higher incidence of grade ≥ 3 cardiac and respiratory toxicities in decitabine-treated AML patients with renal dysfunction (creatinine clearance ≥ 60 mL/min) versus those with normal renal function (creatinine clearance < 60 mL/min) (Levine et al., 2017). No prospective evaluations have been performed.

Patients with a history of severe congestive heart failure or clinically unstable cardiac disease were

excluded from the registration trials of both decitabine and azacitidine (Kantarjian et al., 2012; Dacogen SmPC; Dombret et al., 2015; Vidaza SmPC). Hence, their safety and efficacy in these patients has not been established. Azacitidine has been associated with a significant increase in cardiac events in newly diagnosed AML patients with a history of cardiovascular or pulmonary disease (Vidaza SmPC) and caution is advised when using the drug in these individuals. However, in our experience, both HMAs can be delivered safely to these patients if carefully monitored, because of the lack of direct myocardial toxicity.

6. Predicting response to HMAs

The ability to predict which patients will respond best to HMA treatment would be valuable given that clear signs of response are often not evident for up to 6 cycles (and occasionally longer) (Tawfik et al., 2014; Thépot et al., 2014; He et al., 2017b). This would allow unnecessary and potentially toxic treatment to be avoided. Here we

discuss only AML-related factors although many other variables have been evaluated in MDS.

Multivariate analyses have shown that several baseline clinical factors are associated with reduced OS in AML patients treated with decitabine or azacitidine. In frontline treatment, these include elevated white blood cell count, adverse cytogenetic category, poorer Eastern Cooperative Oncology Group performance status, and increasing age (Mayer et al., 2014; Falantes et al., 2018). In patients with bone marrow blasts ≥ 30% and a white blood cell count < 15,000/μL in DACO-016, median OS was significantly longer with decitabine versus TC (8.6 vs 4.7 months, respectively; HR: 0.67; p = 0.0033) (Kadia et al., 2015). In relapsed/refractory AML, the presence of > 5% circulating blasts or > 20% bone marrow blasts were significant predictors of decreased OS in HMA-treated patients (Stahl et al., 2018a). However, none of these factors is sufficiently predictive of outcomes in AML treated with an HMA relative to other therapies to be used as a baseline biomarker for supporting treatment decision making.

Furthermore, none of these factors can be used to predict the time to response in HMA-treated patients (Boddu et al., 2018a). Hence, although research continues, there is currently no validated clinical marker for predicting response.

Genetic factors may be more useful in predicting potential responders to HMAs. For example, a sub-analysis of data from the DACO-016 study suggested that decitabine may be particularly beneficial in patients with monosomal karyotype, offering significant improvements in median OS relative to TC (6.3 vs 2.6 months, respectively; HR: 0.52; 95% CI: 0.29–0.93; p = 0.025) in a group that normally has a very poor prognosis (Wierzbowska et al., 2018).

Potential associations with improved outcomes with HMAs have also been found in patients with mutations in various genes, including *DNMT3A*, *IDH1*, *IDH2*, *TET2* (Emadi et al., 2015; Tang et al., 2016). However, their predictive value in guiding HMA treatment remains unclear.

Encouraging data have been achieved in HMA-treated patients with an underlying *TP53* mutation, which is associated with a particularly poor prognosis in patients treated with standard induction chemotherapy (Bowen et al., 2009; Rücker et al., 2012). In a study of 116 patients with AML (78%) or MDS (22%) treated with decitabine, response rates were higher among patients with an unfavorable cytogenetic risk profile versus intermediate or favorable cytogenetic profile (67% vs 34%, respectively; p < 0.001), and among patients with *TP53* mutations versus those with wild-type *TP53* (100% vs 41%; p < 0.001) (Welch et al., 2016). In addition, OS was not negatively affected by unfavorable cytogenetics or *TP53* mutation. Furthermore, even outcome after transplant was not influenced by *TP53* mutations in patients receiving decitabine. However, this study was largely based on the more intensive 10-day decitabine regimen rather than the standard 5-day schedule, and hence confirmatory data are required in AML patients treated with the latter. With azacitidine, an exploratory subanalysis of data from AZA-AML-001 suggested that median OS might be longer in patients with *TP53*-mutated AML treated with azacitidine compared with conventional care regimens (7.2 vs 2.4 months, respectively; p = 0.069), although the analysis was underpowered to achieve statistical significance (Tang et al., 2016). Hence, more work is required to better understand the association between *TP53* mutations and outcomes in HMA-treated patients with AML.

It has also been suggested that the type of AML a patient has may impact on outcomes with HMAs. A recent analysis found that among individuals with AML with myelodysplasia-related changes (one of several types of AML defined by the WHO (Döhner et al., 2017)), median OS was significantly prolonged with azacitidine relative to conventional care regimens (8.9 vs 4.9 months, respectively; HR: 0.74; 95% CI: 0.57–0.97) (Seymour et al., 2017). Another population of interest could be those with secondary AML, who typically experience poor outcomes with intensive therapy compared to patients with de novo AML (Granfeldt Østgård et al., 2015; Hulegårdh et al., 2015), and might therefore benefit from alternative treatment strategies. Recent observational data suggested that the median OS of decitabine-treated, elderly AML patients is not influenced by the type of AML (de novo AML, 12.4 months; secondary AML, 16 months; p = 0.8) (Borlenghi et al., 2017).

However, although these observations are interesting and set the stage for future investigations, the choice of therapy with HMAs should not be made solely on the basis of predictive variables that have yet to be validated in larger cohorts of patients.

7. Assessing response to treatment

Once HMA therapy is initiated, it is important to retain patients on the treatment for long enough that response can be accurately assessed. Median times to best response in HMA-treated patients are around 3–5 cycles (Tawfik et al., 2014; Thépot et al., 2014; He et al., 2017b), and a study of azacitidine in newly diagnosed AML showed that 15% of best responses were reached only after > 6 cycles (Thépot et al., 2014). Time to response does not influence OS (Boddu et al., 2018a). Hence, patients should be maintained on HMA treatment for a minimum of 4–6 cycles (Dacogen SmPC; Vidaza SmPC), as long as they experience no serious side effects or clear progressive course in their disease.

A recent meta-analysis of 26 trials in newly diagnosed AML (20 of which involved decitabine or azacitidine) demonstrated a significant correlation between the achievement of complete remission (CR) or CR with incomplete blood recovery (CRi) and median OS (Agarwal et al., 2017). The deepest level of response – measurable residual disease (MRD) negativity – already has an accepted, independent predictive value in AML patients receiving intensive treatment (Döhner et al., 2017); the achievement of MRD negativity has also recently been shown to reduce the risk of relapse in HMA-treated patients (Boddu et al., 2018b).

However, depth of response is not necessarily a good indicator of survival benefit in patients treated with an HMA, and both decitabine and azacitidine can confer an OS benefit in the absence of CR (Dombret et al., 2015; He et al., 2015), contradicting the dogma that achievement of CR as condition of successful therapy in AML. For example, in AZA-AML-001, azacitidine demonstrated an OS benefit compared with conventional care regimens even among those patients who failed to achieve a CR (6.9 vs 4.2 months, respectively; HR: 0.77; 95% CI: 0.62–0.95; p = 0.017) (Dombret et al., 2015). Similarly, in DACO-016, when patients achieving CR were excluded, OS was improved in patients who achieved transfusion independence, suggesting that reaching CR is not a prerequisite for treatment benefit (He et al., 2015). Even long-lasting stable disease (≥ 6 cycles) can confer a significant OS benefit in newly diagnosed AML patients treated with an HMA (Williams et al., 2016).

In a study of 302 AML patients treated with azacitidine, OS was significantly longer in patients who achieved a hematologic improvement compared with those who did not (Pleyer et al., 2014). As noted in recent ELN recommendations (Döhner et al., 2017), HMAs appear to alter the natural course of AML in some patients who do not achieve CR. Hence, hematologic improvement can also yield clinical benefit apart from survival, including reductions in transfusions and improved quality of life (Dombret et al., 2015; He et al., 2015; Döhner et al., 2017).

HMA treatment should therefore be continued for as long as the patient continues to benefit, in the absence of overt disease progression (Dacogen SmPC; Vidaza SmPC). Premature discontinuation of HMA treatment must be avoided. Patients who discontinue therapy after achieving partial or complete remission but before treatment failure may lose their response rapidly after discontinuation (Cabrero et al., 2015). The prognosis following HMA failure is typically poor, with a median OS of less than 6 months (Jabbour et al., 2014).

Given all of the above, if CR is not a good surrogate for survival with HMAs, this raises the question of whether there are any other potential

markers of likely improved survival that can be assessed early during treatment with these drugs. To date, there are none. Several factors have been linked with positive outcomes with HMAs, including platelet response during early cycles of treatment (van der Helm et al., 2011; Jung et al., 2015; Park et al., 2017), early fetal hemoglobin induction (Stomper et al., 2018) decreased need for transfusions (He et al., 2015; Minden et al., 2015), and low numbers of dose modifications (Minden et al., 2015). However, none has been prospectively associated in improved survival. Hence, we do not recommend using any of these to determine whether or not to continue with HMA treatment.

8. Use of HMAs in other settings

8.1. Younger age

HMAs are most often used in older individuals who are unsuitable for intensive chemotherapy. Indeed, the registration trials of decitabine and azacitidine in AML were conducted in patients aged ≥ 65 years (Kantarjian et al., 2012; Dombret et al., 2015). However, in many countries, the indications for both drugs contain no age restrictions (Dacogen SmPC; Vidaza SmPC), and ELN recommendations do not make any age-based differentiation (Döhner et al., 2017). Hence, HMAs should also be considered in younger patients who are not candidates for intensive chemotherapy, for example those with severe comorbidities.

8.2. HMAs pre-hematopoietic stem cell transplant

Independent of age, treatment outcomes in patients with *TP53* mutations, complex karyotype or monosomal karyotype are particularly dismal (Döhner et al., 2017). In these patients, HMAs could be beneficial as a bridge to transplant. The use of HMAs to convert patients from MRD positivity to MRD negativity ahead of transplant is also currently under investigation.

It has been suggested that HMAs could be used as a bridge to transplant in some patients who are not suitable for standard induction chemotherapy. This suggestion is based on the hypothesis that the lower toxicity of these agent reduces upfront mortality and could also enhance the graft-versus-leukemia effect by upregulating human leukocyte antigen expression (Lübbert et al., 2009; Malik and Cashen, 2014). Small studies have demonstrated the feasibility of this approach: a number of patients with newly diagnosed or relapsed/refractory disease who achieved a CR with an HMA successfully proceeded to transplant, despite having been unsuitable for standard induction chemotherapy (Lübbert et al., 2009; Grunwald et al., 2017; Stahl et al., 2018b). Based on these observations, the term of 'inDACtion' has been coined (Michael Lübbert, personal communication, 2009). A Phase 3 study is currently ongoing comparing 10-day decitabine versus standard 7 + 3 induction chemotherapy ahead of allogeneic transplantation (NCT02172872). However, by definition, this trial is being conducted in a cohort of patients that is eligible for intensive chemotherapy. Data from larger studies using HMAs as a bridge to transplant in patients who are not suitable for intensive induction chemotherapy are still awaited.

8.3. Maintenance therapy with HMAs

Maintenance therapy has typically not been considered as a standard element of AML treatment, owing to a lack of evidence of benefit (Döhner et al., 2017). However, there may be a rationale for using HMAs in the maintenance setting, given that they have hypomethylating activity that is distinct from chemotherapy (Blum et al., 2017). Early studies have shown promising results using an HMA as a preventive approach for reducing the risk of relapse post-transplant (de Lima et al., 2010; Goodyear et al., 2012; Pusic et al., 2015). On the flipside, a single-arm study of decitabine as maintenance therapy in 134 younger AML patients (< 60 years) who did not receive allogeneic transplantation in first CR achieved disease-free survival (DFS) rates that were similar to comparable historical controls, suggesting no additional benefit (Blum et al., 2017). However, in a randomized trial of 117 older patients (≥ 60 years) with AML or MDS in CR/CRi after ≥ 2 cycles of intensive chemotherapy, azacitidine maintenance significantly improved DFS relative to observation (12-month DFS: 63% vs 39%, respectively; $p < 0.005$) (Huls et al., 2017). OS was improved with azacitidine after censoring patients who received an allogeneic transplantation (12-month OS: 83% vs 64%, respectively; $p = 0.04$) (Huls et al., 2017). An oral formulation of azacitidine is also being studied in the maintenance setting in a Phase 3 randomized, controlled trial (Roboz et al., 2016); eligible patients are aged ≥ 55 years in first CR, and results are expected in 2019.

8.4. Relapsed/refractory AML

In relapsed/refractory AML, ELN recommendations currently acknowledge that no specific regimen has emerged as the standard of care (Döhner et al., 2017). The efficacy of HMAs has been modest in patients relapsing post-transplant (CR rates of 15–27% and 2-year survival of 12–29%) (Schroeder et al., 2015; Craddock et al., 2016) or with relapsed/refractory disease after intensive chemotherapy (CR rates of 16–21% and median OS of 6–9 months) (Ivanoff et al., 2013; Ritchie et al., 2013; Itzykson et al., 2015; Stahl et al., 2016, 2018a). However, given the paucity of options in these patients, HMAs remain a reasonable choice, particularly in those with no clinical trial alternative.

The use of HMAs, particularly decitabine, to sensitize leukemia cells to further chemotherapy (an approach known as 'epigenetic priming') has also been assessed in small studies in the relapsed/refractory AML setting. Rates of CR/CRi of up to 48% have been achieved, suggesting that this approach may be worthy of further investigation in larger trials (Jain et al., 2016; Halpern et al., 2017).

9. Conclusions

HMAs are a valuable upfront treatment option in AML patients who are not considered to be suitable for intensive chemotherapy, irrespective of age. Treatment should be continued for a minimum of 4–6 cycles to ensure that patients have an adequate opportunity to respond (Dacogen SmPC; Vidaza SmPC). Delivery of insufficient numbers of cycles is a key reason for HMA failure, and premature discontinuation must be avoided. Both of the approved HMAs can confer an OS benefit in the absence of CR (Dombret et al., 2015; He et al., 2015), and hence treatment should continue for as long as the patient achieves benefit, in the absence of overt disease progression (Dacogen SmPC; Vidaza SmPC). Awareness and careful management of AEs may help to ensure sufficient duration of therapy.

Conflicts of interest

VS has received honoraria and funding from Celgene, and honoraria from Janssen, Amgen, Novartis, Otsuka, and AbbVie. GO has received research support from BD, Celgene, Immunogen, Janssen, and Novartis, and has consulted or taken part in advisory boards for Amgen, Astellas, BMS, Celgene, Janssen, Novartis, Pfizer, Roche, Seattle Genetics, and Sunesis.

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Contributions

Both authors contributed to the conception, drafting and revising of the manuscript during preparation, and both gave final approval of the version submitted.

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