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Review article

The role of hypomethylating agents in the treatment of elderly patients with AML

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ABSTRACT

There is a major unmet medical need for treatment options in elderly patients with acute myeloid leukemia (AML) who are deemed ineligible for intensive treatment. The recent approval of decitabine in the European Union for the treatment of patients with AML ≥ 65 years old highlights the potential for hypomethylating agents in this setting. Here, we review evidence to support the use of hypomethylating agents in elderly patients and emphasize the importance of tolerability and quality of life considerations. We focus on the rationale for the continued clinical development of the ribonucleoside analog azacitidine in this setting. We discuss potential differences in the activity of azacitidine and decitabine in different patient subgroups that could possibly be explained by important differences in mechanism of action. Finally, we assess practical challenges that will be faced when integrating hypomethylating agents into clinical practice, such as how to define ineligibility for intensive treatment.

Contents

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1. Introduction

Acute myeloid leukemia (AML) is mostly a disease of the elderly with a median age at diagnosis of ~70 years.[1] Older patients with AML have significant comorbidities, a poorer performance status (PS), more unfavorable cytogenetic abnormalities, and a higher incidence of secondary AML than their younger counterparts.[1]

The decision whether to allocate intensive or non-intensive treatment options to elderly patients with AML (>60 years old) is both challenging and complex and requires careful assessment of disease- and patient-related factors. In some elderly patients, intensive chemotherapy (IC) is an acceptable standard of care, leading to a 45–55% response rate with the potential of improving prognosis.[2–5] However, long-term survival generally remains low due to a higher risk of relapse and treatment-related mortality compared with younger patients.[6] Patients deemed 'unfit' or ineligible for IC are frequently offered best supportive care (BSC) only. Unfortunately, prognosis in untreated elderly patients is dismal. In a Surveillance, Epidemiology, and End Results cancer registry analysis, median survival in 2657 adults ≥65 years was 2 months and the 2-year survival rate was 6%. For untreated patients, median survival was 1 month compared to 7 months for the 30% of patients who received chemotherapy.[7] Alternatively, some frail patients are offered low-dose cytarabine (LDAC). Although more tolerable than IC, outcomes with LDAC are generally poor with a median survival time of only 4 months.[8] Therefore, there is an unmet need for well tolerated treatment options for these patients.

Hypomethylating agents (HMA) may have the potential to improve survival and quality of life in elderly patients with AML. Indeed, quality of life and patient-reported outcomes are key considerations when selecting appropriate treatment for the elderly.[9]

There is biological rationale for assessing HMA in these patients. Recent studies have demonstrated that gene hypermethylation is widespread in patients with AML and is implicated in the pathogenesis and progression of the disease.[10] Moreover, extensive clinical experience with two HMA, azacitidine and decitabine, has demonstrated that the drugs are well tolerated in elderly and frail patients.[11–14]

In this review, we discuss available efficacy and safety data for both azacitidine and decitabine in patients with AML, as well as current understanding of the mechanism of action of these drugs. Furthermore, we assess the challenges that will be faced when integrating HMA into clinical practice, such as how to define ineligibility for IC.

2. Hypomethylating Agents in Elderly Patients with AML: Phase III Studies

Both decitabine and azacitidine have been, or are being, assessed in phase III studies in elderly patients with AML (DACO-016 and AZA-AML-001 trials, respectively).

2.1. *DACO-016 Study*

The recently published DACO-016 study compared the efficacy and safety of decitabine (20 mg/m^2/day for 5 days every 4 weeks) versus treatment choice (TC; LDAC [20 mg/m^2/day for 10 days every 4 weeks] or BSC) in 485 patients who were deemed ineligible for IC.[15] The primary endpoint was overall survival (OS); secondary endpoints included complete remission (CR) rate and adverse events (AEs). The median age of patients enrolled onto the DACO-016 trial was 73 years; 35% of patients had secondary AML, 36% had poor-risk cytogenetics and 24% had an Eastern Cooperative Oncology Group (ECOG) PS of 2.

The preplanned primary efficacy analysis was undertaken in October 2009 following 396 deaths (Fig. 1). This analysis demonstrated a non-significant trend towards improved OS in the decitabine arm versus TC (7.7 vs 5.0 months; $p = 0.108$). A year after the initial analysis, an unplanned ad hoc efficacy analysis was performed following 446 deaths. The median OS for both arms was the same as in the initial analysis, but the difference between the decitabine arm and the TC arm was now nominally significant ($p = 0.037$; Fig. 1).[15] Following adjustment for study drug exposure, the overall death rate (per patient year) was lower for decitabine than for LDAC (0.57 vs 0.73). Based on a subanalysis of the trial, decitabine has not shown any evidence of improving OS in patients with 20–30% blasts. Incidence of AEs was similar between arms. The most common grades 3–4

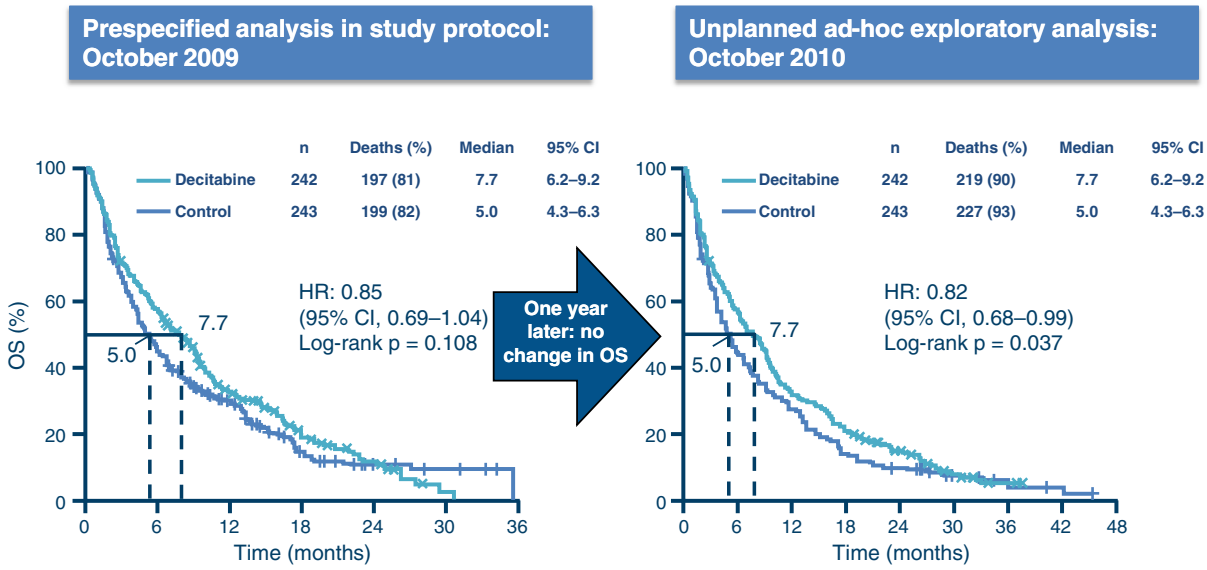

Fig. 1 – Predesignated and ad-hoc analyses of overall survival in the DACO-016 trial. [15]

treatment-emergent AEs were thrombocytopenia and anemia. Drug-related AEs occurred in 74% of patients treated with decitabine and 73% of patients treated with LDAC with the most common being thrombocytopenia (27%), anemia (21%), neutropenia (24%) and febrile neutropenia (21%).

Decitabine was recently approved by the European Medicines Agency (EMA) for the treatment of AML in patients aged ≥65 years with de novo/secondary AML who are not candidates for IC.[16] In contrast, the US Food and Drug Agency (FDA) Oncologic Drugs Advisory Committee (ODAC) did not recommend approval of decitabine based on concerns regarding the statistical validity and robustness of the data. Several issues including the interpretation of the data of the TC arm of the trial were raised. For example, patients who received BSC, although few in number (n = 28), were grouped together with patients treated with LDAC when TC was compared to decitabine. The negative impact of this fact on OS in the TC arm could not be excluded. The FDA ODAC highlighted a number of concerns regarding the results of DACO-016 which, in their view, precluded marketing approval: i) a lower than expected response rate in the LDAC arm; ii) inexplicable variation in efficacy across different geographical regions; in Western Europe, for example, the CR rate with LDAC was higher than the response rate with decitabine. iii) unplanned and exploratory ad hoc analysis of OS; iv) failure to achieve primary endpoint. Additionally, concerns regarding the lack of strict criteria for entry to the study were expressed. About 10% of patients who supposedly were deemed not to be fit for IC ultimately received IC following randomization in the study. This may encourage some physicians to use decitabine in patients who may be better candidates for IC.[9,17]

2.2. AZA-AML-001 Study

In the ongoing AZA-AML-001 trial, patients (target enrolment of 480 patients) were randomized 1:1 to receive either azacitidine (75 mg/m^2/day for 7 days every 4 weeks) or conventional care regimen (CCR; BSC, LDAC [40 mg/day for 10 days every 4 weeks] or IC). Choice of CCR was assigned by the treating physician. The primary endpoint of AZA-AML-001 is OS. Secondary endpoints include remission rate, event-free survival, safety and, importantly, patient-reported quality of life outcomes. Inclusion criteria for AZA-AML-001 were similar to DACO-016, although there were some notable differences. Firstly, patients in the control arm of AZA-AML-001 could receive IC, LDAC or BSC rather than just LDAC or BSC. Secondly, a bone marrow (BM) blast count of >30%, rather than ≥20%, was required.

The AZA-AML-001 trial is scheduled to be completed (including final data collection for primary outcome measure) late 2013. These data will be instrumental in defining the future role of azacitidine in patients with AML and >30% blasts. Azacitidine is already approved for the treatment of patients with AML and 20–30% blasts, based on a subanalysis of the phase III AZA-001 trial (described below).[11]

2.3. AZA-001 Study

The AZA-001 trial compared the efficacy and safety of azacitidine with CCR (BSC, LDAC, IC) in 358 patients with predominantly int-2-/high-risk MDS.[18] However, 113 patients with WHO-AML (20–30% blasts) were also included.[11] The efficacy population included 55 patients randomly assigned to azacitidine and 58 patients randomly assigned to CCR. Of the 58 patients in the CCR group, 27 (47%), 20 (34%), and 11 (19%) were preselected by their treating physicians to receive BSC, LDAC, and IC, respectively. Baseline characteristics were comparable between the two treatment groups. In these patients: i) azacitidine halved the risk of death compared with CCR. After a median follow-up of 20.1 months, OS was 24.5 months in the azacitidine group and 16.0 months in the CCR group (HR [95%CI] = 0.47 [0.28–0.79]; p = 0.005; Fig. 2); further, a survival comparison between azacitidine vs CCR according to investigator pre-selection was conducted. A significant difference in OS favoring azacitidine (n = 36) vs BSC (n = 27), with median OS of 19.1 vs 13.4 months, respectively (p = 0.03) was detected. Median OS for azacitidine (n = 14) was 24.5 vs 17 months for LDAC (n = 20) (p = 0.08). Median OS was

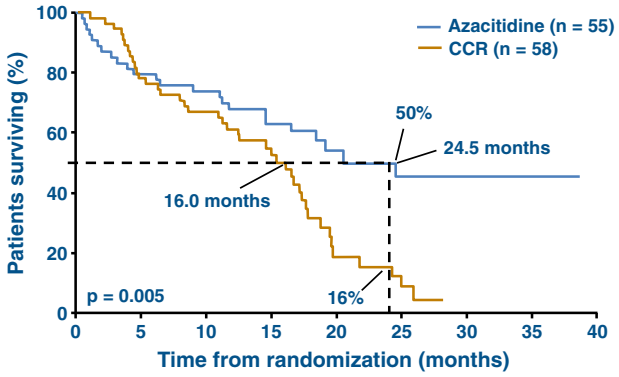

Fig. 2 – AZA-001: Overall survival in WHO-defined patients with AML (20–30% blasts). [11]

not reached for azacitidine (n = 5) compared with 14.2 months for IC (n = 11) ($p = 0.97$). Although interesting, the data must be interpreted with caution because of the small number of patients in each CCR regimen. ii) Significantly more patients who were red blood cell transfusion-dependent (RBC-TD) at baseline achieved transfusion independence with azacitidine compared with CCR (41% vs 18%, respectively; $p = 0.04$); iii) AEs were generally predictable (predominantly hematological, gastrointestinal or injection site reactions) and manageable on treatment; iv) the CR rate in the azacitidine arm was 18% compared with 16% in the CCR arm, indicating that CR is not a prerequisite for survival benefit in patients treated with azacitidine.

Based on this analysis, azacitidine has become established as a treatment option in patients with WHO-AML (20–30% blasts) who are ineligible for intensive treatment.

3. Hypomethylating Agents in Elderly Patients with AML: Phase II Studies

To date, there are no prospective data available that directly compare the efficacy and safety of azacitidine and decitabine in patients with AML. To date, three phase II studies have been reported for decitabine in patients with AML (all first-line elderly patients deemed ineligible for IC; Table 1). [19–21] One phase II study of azacitidine monotherapy in patients with AML (in both first-line and relapsed/refractory patients) has been published.[22]

Our study assessed the efficacy and safety of azacitidine (75 mg/m^2/day for 5 days every 28 days) in patients with AML and ≥20% BM blasts who were deemed medically unfit for IC, based on comorbidity profile. [22] The study demonstrated that azacitidine was generally well tolerated; all treatment-related AEs were reversible and effectively managed with supportive measures and dose delays. Median OS in patients treated with first-line azacitidine (7.7 months) compared favorably with OS rates historically achieved with LDAC (median survival of 4 months).[8] Median OS in patients who achieved stable disease (SD) was 10 months, which was similar to that achieved in patients with CR, partial response (PR) or hematological improvement (HI). Again, these data suggest that CR is not a prerequisite for improved survival in patients with AML given azacitidine, as is also the case in patients with MDS and WHO-AML (20–30% blasts).[11,18] The response rate in patients with previously untreated AML was 50%. There was also some evidence of clinical activity in patients with relapsed/refractory AML (response rate of 10%). An important observation was that hematological responses were rapid (median time to response was 2.5 months); furthermore, early reductions in BM blast count by day 15 of the first cycle were highly predictive of subsequent response.[22] This suggests that azacitidine elicits early anti-leukemia responses, which is clearly an important consideration when treating patients with high-risk disease and very dismal prognosis.

Based on the three published phase II decitabine studies (Table 1) survival with azacitidine seems comparable with that observed in decitabine trials which reported median OS ranging from 5.5 months to ~1 year and 1-year OS of ~30–50%. However, it is not possible to come to any definitive conclusions regarding the relative efficacy and safety of the two drugs based on these small phase II studies.

4. Hypomethylating Agents in Elderly Patients with AML: Retrospective Studies

A number of retrospective single-center studies or national/international patient registries have assessed HMA in patients with AML (Tables 2, 3). The majority of these studies reported outcomes in patients treated with azacitidine (Table 2) and are the focus of the following discussion.

Most studies demonstrated that response to azacitidine was strongly associated with prolonged OS.[23,24] Furthermore, as in the phase II trial, any kind of response to azacitidine appeared to be sufficient to confer a survival advantage. For example, in a study of 128 patients treated with azacitidine, Pleyer et al. demonstrated that achievement of any kind of HI was associated with longer OS than that observed in patients who did not achieve HI (18.9 vs 6.0 months; $p < 0.001$).[25]

Given the heterogeneity of AML, retrospective studies of large cohorts of patients may be invaluable for generating hypotheses regarding the appropriate patient population to be treated with HMA. It is important to note that the retrospective studies listed in Tables 2 and 3 encompassed a wide range of AML patients with diverse risk factor profiles. For example, in patients treated with azacitidine, the following characteristics ranged from: ECOG PS ≥2: 0–67%; secondary AML: 20–51%; poor-risk cytogenetics: 18–55%; median BM blast count: 34–70%. Clearly, many patients included in the retrospective studies had high-risk disease. The impacts of specific disease- and patient-related characteristics on clinical outcome in AML patients treated with azacitidine are discussed below.

5. Impact of Patient-Related Factors on Treatment Choice in Elderly Patients with AML

5.1. *Age*

Increased age is a negative prognostic factor in patients with AML but should not be considered in isolation. PS and comorbidities must also be considered when deciding treatment. [3] Importantly, in several retrospective studies, age per se did not predict OS in AML patients treated with azacitidine. [25,26]

The median age of the patients in these studies was ~75 years old, which reflects the typical AML population. Similarly, the median age in the DACO-016 trial was 73 years.[15] Most patients in this age range would be deemed ineligible for IC. Furthermore, even in those patients deemed eligible, IC will only benefit approximately a third of those who receive it.[27] These observations, in addition to disappointing OS in elderly patients treated with LDAC,[8] indicate that HMA could become a promising future treatment option in very elderly patients.

5.2. *Comorbidities*

Comorbidities are highly prevalent in elderly patients and influence treatment decisions.[28] In AML management, the impact of comorbidities is poorly defined and often complicates treatment decisions. While many comorbidity indices have emerged in oncology, none have been validated on a large scale in the management of elderly patients with AML. Comorbidity scoring could be helpful in identifying subgroups of elderly patients who are likely to tolerate or benefit from IC.[29] It is encouraging to note that azacitidine appears to be active in elderly patients regardless of comorbidity burden. Pleyer et al. demonstrated that the absolute number of comorbidities had no effect on OS. Furthermore, OS in patients according to low-, intermediate- and high-risk comorbidity scores (based on hematopoietic cell transplantation comorbidity index) was 10.2, 9.0 and 9.7 months, respectively.[25] These data suggest that the presence of comorbidities should not lead to a decision to withhold treatment with HMA in favor of BSC in elderly patients with AML.

5.3. *Performance Status*

Performance status (PS) is a frequently used parameter to quantify a patient's activities of daily life, and determine whether the patient is eligible for IC. Patients with PS >2 are often excluded from clinical trials in which patients are to be treated with IC; according to ECOG, it is generally plausible to include patients up to 75 years old with no comorbidities and a PS of 0–1 in such trials.[30] HMA might be an option for patients with poor PS. As expected, most studies demonstrated that elevated ECOG-PS was associated with poorer OS in patients treated with azacitidine.[25,31] Importantly, however, the AZA-AML-001 trial will be stratified according to ECOG-PS and this will determine whether azacitidine offers a survival advantage over conventional treatment options in patients with high ECOG-PS. In the DACO-016 trial, the subgroup of patients with an ECOG-PS of 2, but not 0–1, had significantly improved survival when treated with decitabine versus TC.[15]

6. Impact of Disease-Related Factors on Treatment Choice in Elderly Patients with AML

6.1. *Cytogenetics*

Adverse cytogenetics are associated with poor response rates and shorter survival in patients treated with IC [32–35] and LDAC.[8]

With HMA, survival is also superior in patients with intermediate- compared to high-risk cytogenetics.[15,25,26] Nevertheless, in patients with unfavorable cytogenetics included in the AZA-001 trial, median OS was 12.3 and 5.3 months, respectively, in the azacitidine and CCR arms ($p = 0.38$). The 2-year OS rate was 38% and 16%, respectively ($p = 0.001$).[11] In the DACO-016 trial, the survival data were in favor of decitabine compared with TC for patients with poor-risk cytogenetics. [15]

6.2. *'Proliferative' AML*

Based on available data it remains unclear whether HMA could potentially be effective in highly proliferative AML. Patients with a white blood cell (WBC) count of $\geq 15 \times 10^9$/L were excluded from AZA-AML-001. In contrast, patients with a WBC count of $\leq 40 \times 10^9$/L were eligible for DACO-016, although the median WBC count of enrolled patients was 3.4×10^9/L (range: 0.3–127.0);[15] only 24% of patients had a WBC count of $\geq 10 \times 10^9$/L. Some retrospective studies have suggested that patients with a WBC count of $\geq 10 \times 10^9$/L benefit less from azacitidine than those with lower WBC counts.[36] Conversely, other studies have found that WBC count did not impact OS in patients with AML treated with azacitidine.[25,26]

Furthermore, it is unclear whether a given BM blast threshold has any clinical significance. For example, in several studies, the OS of patients treated with IC was not significantly different in patients with 20–30% blasts compared with patients with >30% blasts.[37–39] Likewise, some emerging clinical trial data suggest that HMA are effective in patients with >30% blasts. In DACO-016, decitabine improved survival in patients with >30% blasts.[15] Except one study,[31] retrospective data have indicated that blast count (>30% vs ≤30%) at baseline did not predict OS in elderly patients treated with azacitidine.[25,36]

6.3. *Type of AML*

Incidence of secondary AML from an antecedent hematological disorder (AHD) or previous exposure to chemotherapy and/or radiation (therapy-related AML), increases with age and is associated with poor outcomes irrespective of age, cytogenetic risk, PS or whether patients receive IC. Even for patients <65 years old treated with IC, median OS is only 7–9 months.[40] It is clear, therefore, that there is an unmet clinical need for new treatment options in secondary AML. Possibilities include HMA and allogeneic hematopoietic stem cell transplantation using reduced-intensity conditioning (HCT-RIC).

Few data are available regarding the efficacy of HMA in secondary AML. In the DACO-016 trial, 36% of enrolled patients suffered from secondary AML. There was a trend towards improved survival in patients given decitabine versus TC which did not achieve statistical significance.[15] In azacitidine studies, 20–51% of patients had secondary AML (Table 2). A recent retrospective study of 26 patients with AML secondary to Philadelphia-negative myeloproliferative neoplasms indicated that azacitidine was associated with a promising response rate of 38% and an OS of 8 months.[41]

Table 1 – Summary of phase II trials of decitabine and azacitidine in patients with AML.

Study	Inclusion criteria	Baseline characteristics	Treatment	Response	Survival	Safety
Lubbert et al.[21]	• First-line patients • >60 years old • ECOG PS: 0–2 • >30% blasts • Any cytogenetics	• Patients, n: 227 • Median age, years (range): 72 (56–86) • ECOG PS, 0/1/2, %: 19/58/22 • HCT-CI, 0/1–2/>3, %: 21/42/37 • AML type, p/s: 49/51 • Median WBC, $\times 10^9$/L (range): 4.4 (<1–241) • Median blasts,%: 56 (10–100)	• Decitabine 135 mg/m^2 total dose every 6 weeks • ATRA given to 100 patients during cycle 2 • Median cycles, n (range): 2 (1–4)	• ORR: 52% • CR: 13% • PR: 13% • HI: 26%	• Median OS, months: 5.5 • 1 year OS, % (95% CI): 28 (22–34) • Parameters associated with worse outcome: low platelets, age, ECOG-PS and high LDH	• Grade 3–4 neutropenia, %: 51 • Grade 3–4 thrombocytopenia, %: 51
Cashen et al.[20]	• First-line patients • >60 years old • Int/poor cytogenetics • ECOG PS: 0–2 • Ineligible for IC or HCT • >20% blasts	• Patients, n: 55 • Median age, years (range): 74 (61–87) • ECOG PS, 0/1/2: 47/35/18 • Cytogenetics, int/poor/na: 53/45/2 • AML type, p/s/t: 55/35/7 • Median WBC, $\times 10^9$/L: 2.7 (1–111) • Median blasts,%: 50 (0–99)	• Decitabine 20 mg/m^2 for 5 days every 4 weeks • Median cycles: 3 (1–25)	• ORR: 25% • CR: 24% • CRi: 2% • SD: 29% • Failure: 31% • n/a: 15% • Median time to response, days: 126 (4.5 cycles)	• Minimum follow up: 1 year • Median OS, months (95% CI): 7.7 (5.7–11.6) • Median EFS, months (range): 5.8 (3 days to 23.6 months) • Median OS in responders, months: 14 • Factors that predicted short survival: ECOG PS of 2, male gender, high blasts	• Grade 3–4 neutropenia, %: 20 • Grade 3–4 febrile neutropenia, %: 29 • Grade 3–4 thrombocytopenia, %: 22 • Delayed cycles, %: 27 • Dose reductions: uncommon
Blum et al.[19]	• First-line patients • ≥60 years old • Ineligible or refused IC • WBC <40 × 10^9/L	• Patients, n: 53 • Median age, years (range): 74 (60–85) • MRC prognostic score, good/standard/poor: 19/32/49 • Cytogenetics, normal/complex/other: 40/30/26 • AML type, p/s/t: 64/25/11 • Median WBC, $\times 10^9$/L (range): 2.7 (0.4–150) • Median blasts,% (range): 52 (20–92)	• Decitabine 20 mg/m^2 for 10 days every 4 weeks (dose subsequently reduced if blasts <5% or if grade 4 neutropenia experienced) • Median cycles, n (range): 4 (1–21+)	• ORR: 64% • CR: 47% • CRi: 17% • CR in patients with WBC ≥15 × 10^9/L: 57% • CRs occurred in all cytogenetic subgroups	• Median OS, weeks (95% CI): 55 (36–72) • Median DFS, weeks (95% CI): 46 (30–NR) • Four patients received non-myeloablative HCT after CR	• Grade 3–4 febrile neutropenia, %: 68 (during first two cycles)

Al-Ali et al. (first-line)[22]	• ≥18 years old • Ineligible or refused IC • ≥20% BM blasts • Medically unfit for induction chemotherapy • Patients either had serious comorbidity, or severe uncontrolled infections	• Patients, n: 20 • Median age, years (range): 78 (64–84) • Cytogenetic risk, int/high, %: 75/25 • AML type, p/s, %: 40/60 • Median WBC, $\times 10^9$/L (range): 3.4 (0.8–187) • Median blasts, % (range): 44 (10–90)	• Azacitidine 75 mg/m^2 for 5 days every 4 weeks until progressive disease or relapse • Median cycles, n: 6	• ORR: 50% • SD: 25% • PD: 0% • Early death: 25% • Median time to response, months (range): 3.5 (2–7) • Median duration of response; months (range): 5.5 (1–NR)	• Median follow-up, months (range): 13 (9–16) • Median OS, months (range): 7.7 (0.2–NR) • OS similar between pAML and sAML • OS in responding patients: not reached • OS in patients with SD, months: 10 • 1 year OS, %: 39	• Grade 3/4 thrombocytopenia,%: ~70 • Grade 3/4 neutropenia, %: ~65 • Hematological AEs were reversible in all patients, mainly by dose delays • Delayed cycles, %: 11 • Patients requiring dose reduction, %: 13 • Non-hematological AEs were generally mild and manageable
Al-Ali et al. (second-line)[22]	• Same as above	• Patients, n: 20 • Median age, years (range): 67 (32–83) • Cytogenetic risk, int/high, %: 65/35 • AML type, p/s/NA, %: 70/25/5 • Median WBC, $\times 10^9$/L: 3.6 (0.7–36) • Median blasts, %: 40 (15–80) • Relapsed/refractory,%: 65/35	• As above, except median cycles, n: 2	• ORR: 10% • SD: 50% • PD: 10% • Early death: 30% • Median time to response, months (range): 1.5 (1–2) • Median duration of response; months (range): 4.5 (4–5)	• Median follow-up, months (range): 13 (9–16) • Median OS, months (range): 2.9 (0.7–NR) • OS similar between refractory and relapsed patients	• Grade 3/4 thrombocytopenia,%: ~70 • Grade 3/4 neutropenia, %: ~65 • Hematological AEs were reversible in all patients, mainly by dose delays • Delayed cycles, %: 11 • Patients requiring dose reduction, %: 13 • Non-hematological AEs were generally mild and manageable

ATRA: all-trans retinoic acid, CR: complete response, EFS: event free survival, HI: hematological improvement, LDH: lactate dehydrogenase, n/a: not available, NR: not reported, mCR: complete marrow response, ORR: overall response rate, OS: overall survival, p: primary, PD: progressive disease, PR: partial response, s: secondary, and t: therapy-related.

Table 2 – Overview of retrospective studies of azacitidine in patients with AML.

Study	Baseline characteristics	Treatment	Response	Survival
a) Patients with previously untreated AML				
Bories et al.[26]	• Patients, n: 98 • Median age, years (range): 76 (60–89) • ECOG PS, ≥2, %: 29 • AML type, p/s: 72/28 • WBC, >10 × 10^9/L, %: 14 • Median blasts,% (range):35 • (0–99) • Cytogenetics, int/poor, %: 49/45	• Azacitidine 75 mg/m^2/day for 7 days every 28 days • Median cycles, n (range): 6 (1–27)	• ORR: 51% • CR: 13% • CRi: 5% • PR: 6% • HI: 27% • Median cycles to best response, n: 6	• Median OS, months: ~12 • 1 year OS, %: 50 • Parameters associated with worse OS (multivariate): high LDH, adverse cytogenetics • Parameters with no effect on OS (multivariate): age, ECOG PS, WBC
Serrano et al.[23]	• Patients, n: 67 • Median age, years (range): 71 (60–84) • ECOG PS, ≥2, %: 67 • Cytogenetics, int/poor, %: 69/22 • AML type, p/s, %: 49/51 • Median WBC, ×10^9/L (range): 4.4 (0.2–18) • Median blasts,% (range): 34 (20–84)	• Azacitidine 75–100 mg/m^2 for 7 days every 4 weeks • Median cycles, n (range): 6 (1–24)	• ORR: 38% • CR: 13% • PR: 13% • HI: 16%	• Median follow up, months (range): 7.4 (1–28.3) • Median OS, months: 13.7 • OS was significantly higher in patients who responded than patients who did not respond • OS was significantly higher in patients with HI than patients who did not respond
Sudan et al.[24]	• Patients, n: 20 • Mean age, years (range): 68 (44–80) • Cytogenetics, normal/simple/complex, %: 35/25/40 • ECOG ≤1, %: 100 • Median WBC, ×10^9/L (range): 4.0 (0.65–105) • Blasts, ≥30%, %: 40	• Azacitidine 75 mg/m^2/day for 7 days every 4 weeks	• ORR: 60% • CR: 20% • PR: 25% • HI: 15% • Median time to response, months (range): 3 (2–5) • RBC-TI: 61%	• Median survival in responders, months (range): 15+ (10–36+) • Median survival in non-responders, months: 2.5 • No significant difference in OS between patients who achieved CR/PR and those who achieved HI
Maurillo et al.[36]	• Patients, n: 35 • Median age, years (range): 77 (46–87) • Cytogenetics, int/poor/fail, %: 37/23/40 • AML type, p/s/t, %: 77/20/3 • Median WBC, ×10^9/L (range): 4.0 (0.65–105) • Median blasts,% (range): 35 (20–80)	• Azacitidine 75 mg/m^2/day for 7 days every 4 weeks: 66% • Azacitidine 100 mg/day for 7 days every 4 weeks: 34% • Median cycles, n (range): 6 (1–18)	• ORR: 48% • CR: 23% • CRi: 8% • PR: 17% • SD: 23% • Median duration of response, months: 6	• Median follow up, months: 12 • Median OS, months: 9 • 1 year OS, %: 35 • Median OS in responders, months: 13 • Median OS in non-responders, months: 5 • Elevated WBC count (>10^9/L) was associated with poor survival (4 vs 9 months; p = 0.011) • No significant difference in OS in patients with <30 and ≥30% blasts
Ramos et al.[31]	• Patients, n: 110 • Median age, years (range):75 (56–89) • Cytogenetics, favorable/int/adverse, %: 1/58/27	• Median dose: 73.6 mg/m^2/day • 7-day schedule: 64% • Median cycles, n (range):4(1–29)	• Median follow-up, months: 8.6 • ORR: 45% • CR: 16%	• Median OS, months: 8.1 • 1 year OS, %: 37 • OS was significantly higher in patients who responded than patients who did not respond, in patients with ECOG ≤1 and in patients with BM blasts ≤30%

	• ECOG ≥2, %: 30 • sAML, %: 55 • Comorbidities, %: 87			
b) Patients with previously untreated or relapsed/refractory AML				
Gavillet et al.[51]	• Patients, n: 38 • Median age, years (range): 68 (25–86) • Cytogenetics, favorable/int/poor, %: 8/64/29 • AML type, p/s/rr, %: 42/45/13 • Median WBC, $\times 10^9$/L (range): 3.1 (0.6–37) • Median blasts, % (range): 70 (20–90) • Baseline or acquired RBC-TI, %: 58%	• Azacitidine 100 mg/m^2/day for 5 days every 4 weeks • Median cycles, n (range): 6 (3–20)	• ORR: 23% • CRi: 18% • PR: 5%	• Median OS in RBC-TI patients, months: 11.1 • 1 year OS in RBC-TI patients, %: 40 • Median OS in RBC-TD patients, months: 5 • 1 year OS in RBC-TD patients, %: 13 • Parameters associated with worse OS (multivariate): RBC-TD • Parameters with no effect on OS (multivariate): peripheral blasts ≥20%, relapsed/refractory disease
Pleyer et al.[25]	• Patients, n: 155 • Median age, years (range): 73 (33–91) • Cytogenetics (IPSS), good/int/poor, %: 59/16/17 • Prior chemotherapy, y/n: 39/61 • AML type, p/s/t, %: 37/48/10 • WBC, >10 × 10^9/L, %: 21 • Blasts, >30%, %: 63 • ECOG PS >1, %: 26 • Comorbidities, 0-1/2-3/>3, %: 43/39/18	• Azacitidine 75 mg/m^2/day for 7 days every 4 weeks: 57% • Azacitidine 75 mg/m^2/day, 5-2-2 schedule every 4 weeks: 22% • Azacitidine 75 mg/m^2 for 5 days every 4 weeks: 16% • Other: 5% • Median cycles, n (range): 4 (1–24)	• ORR: 45% • CR: 10% • mCR: 3% • PR: 21% • SD with HI: 3% • HI only: 9% • RBC-TI (in patients RBC-TD at baseline; n = 97): 36% • Median time to response, months: 4	• Median OS from initiation of azacitidine, months: 9.8 • Median OS according to o RBC-TI: 19.3 vs 9.6 months o HI: 18.9 vs 6.0 months o CR/SD/PD: 24.7 vs 15.2 vs 2.3 months • Parameters associated with worse OS (multivariate): no HI, no (any) response to azacitidine, intermediate or high 'Itzykson' prognostic score [94] • Parameters with no effect on OS (multivariate): age, WBC count, BM blasts, number of comorbidities, prior IC
c) Patients with relapsed/refractory AML				
Maurillo et al.[36]	• Patients, n: 47 • Median age, years (range): 67 (29–81) • Cytogenetics, int/poor/fail, %: 66/21/13 • AML type, p/s/t, %: 60/38/2 • Median WBC, $\times 10^9$/L (range): 8.0 (0.60–85) • Median blasts,% (range): 30 (20–90)	• Azacitidine 75 mg/m^2/day for 7 days every 4 weeks: 38% • Azacitidine 100 mg/day for 7 days every 4 weeks: 62% • Median cycles, n (range): 4 (1–22)	• ORR: 19% • CR: 8% • CRi: 3% • PR: 8% • HI: 6% • SD: 30% • Median DOR, months: 5	• Median follow up, months: 12 • Median OS, months: 7 • 1 year OS, %: 18 • Median OS in responders, months: 8 • Median OS in non-responders, months: 7

BM: bone marrow, CR: complete response, CRi: complete response with incomplete blast recovery, DOR: duration of response, ECOG PS: European Cooperative Oncology Group performance status, HI: hematological improvement, IC: intensive care, IPSS: international prognostic scoring system, LDH: lactate dehydrogenase, mCR: complete marrow response, ORR: overall response rate, OS: overall survival, p: primary, PD: progressive disease, PR: partial response, RBC-TD: red blood cell transfusion dependence, RBC-TI: red blood cell-transfusion independence, rr: relapsed/refractory, s: secondary, SD: stable disease, t: therapy-related, and WBC: white blood cells.

Table 3 – Overview of retrospective studies of decitabine in patients with AML.

Study	Baseline characteristics	Treatment	Response	Survival
a) *Patients with previously untreated AML*				
Gourdin et al.[99]	• Patients, n: 32 • Median age, years (range): 74 (52–86) • ECOG PS, ≥2, %: 31 • Karyotype, unfavorable/int/na, n: 17/14/1 • Comorbidities, %: 100	• Decitabine 20 mg/m^2/day for 10 days • Subsequent 5-day cycles until disease progression if patients attained <5% BM blasts • Median cycles, n (range): 2 (1–4)	• ORR: 31% • CR: 28% • PR: 3%	• Median DFS, days (range): 390 (87 + −468+) • Median OS, days (range): 180 (15–623+) • 6 month OS, %: 37.5 • 1 year OS, %: 16.5
b) *Patients with previously untreated or relapsed/refractory AML*				
Ganetsky et al.[52]	• Patients, n: 60 • Median age, years (range): 62 (28–80) • Prior chemotherapy, y/n, %: 78/22 • Of patients who received prior chemotherapy: • Mean chemotherapy regimens: 2.5 • Post HCT: 30%	• Decitabine 20 mg/m^2/day for 5 days	Overall • ORR: 13% • CR: 12% • PR: 2% • Mean cycles to achieve maximal response, n: 3.25 Relapsed/refractory AML • CR: 8.5% Untreated • CR: 23%	• Not reported
c) *Patients with relapsed/refractory AML*				
Fernandez et al.[100]	• Patients, n: 9 • Median age, years (range): 59 (40–83) • AML type, primary, % 100 • Median BM blasts, % (range): 22 (7–73) • Cytogenetics, normal/int/poor, n: 2/3/4	• Decitabine 20 mg/m^2/day for 5 days every 4–5 weeks • Median cycles, n (range): 6 (1–12)	• CR: 56% • PR: 22% • PD: 22% • Median TTP, months (range): 11 (1–20)	• Median OS, months (range): 12 (10–20)
George et al.[53]	• Patients, n: 19 • Median age, years (range): 61 (22–78) • All patients had intermediate or poor risk cytogenetics • >3 chemotherapy regimens, %: 79% • Post HCT, %: 21	• Decitabine 20 mg/m^2/day for 5 days • Median cycles, n: 2	• No patients achieved CR or CRi • Discontinuation due to disease progression or death, %: 95	• Median OS, months: 3.1 • Mortality at 30 days, n: 0

CR: complete response, DFS: disease free survival, HCT: hematopoietic stem cell transplantation, ORR: overall response rate, OS: overall survival, PD: progressive disease, PR: partial response, SD: stable disease, and TTP: time to progression.

7. Impact of Treatment-Related Factors in Elderly Patients with AML

7.1. Achieving Complete Response

Irrespective of age, long-term survival of patients with AML treated with IC depends on the ability to clear BM blasts at an early stage and induce a CR.[42,43] Similarly, in patients with AML treated with LDAC, OS is strongly associated with achievement of CR.[8] By contrast, one of the observations regarding azacitidine is its apparent ability to offer a survival advantage in elderly patients with AML who achieve any kind of hematological response, regardless of whether CR is achieved.[22,25] In a palliative setting, the translation of any hematological response, not only CR, into improved survival might establish a new paradigm in the treatment of AML, especially in the elderly.

7.2. Maintenance or Post-Remission Therapy

Controversies exist regarding the role of post-remission chemotherapy in improving long-term survival in elderly patients with AML. Several studies have indicated that subsequent cycles of induction chemotherapy following achievement of CR offered no benefit to patients. [3,44,45] By contrast, early clinical data suggest that maintenance therapy with azacitidine may benefit some patients with AML, MDS or chronic myelomonocytic leukemia (CMML).[46] In a phase II study, 23 patients with AML/

MDS/CMML who had reached CR with induction chemotherapy received azacitidine as maintenance therapy; median duration of CR was 13.5 months. Of particular interest was a subgroup of 4 patients with a karyotype including trisomy 8, who all achieved CR with durations of 18–30.5 months. Furthermore, as with MDS,[47] evidence suggests that a proportion of AML patients who respond to azacitidine go on to achieve a better response with continued treatment.[25] Also, it is likely that termination of treatment with azacitidine following a response could lead to rapid relapse as has recently been observed in patients with MDS.[48] Indeed, given the reversible nature of epigenetic modifications, it is likely that continuous treatment with azacitidine is required in patients with AML, though this assertion requires substantiation in prospective clinical trials.

7.3. *Relapsed or Refractory AML*

There is no standard of care for relapsed/refractory AML following chemotherapy. The prognosis is generally very poor.[49,50]

Several retrospective studies have assessed azacitidine in this setting. Some studies have reported superior outcomes in first-line versus relapsed/refractory patients. For example, Maurillo et al. reported an overall response rate (ORR) of 48% vs 19%, respectively, in the two groups ($p = 0.006$) which translated into an OS of 9 months vs 7 months. [36] Other studies have demonstrated similar outcomes in first-line versus relapsed/refractory patients treated with azacitidine.[51]

Results from retrospective studies suggest that decitabine may have limited clinical activity in patients with relapsed/refractory AML. In a study of 47 patients treated with decitabine in a salvage setting, only 4 patients achieved a CR.[52] Similarly, in a retrospective study of 19 patients with relapsed/refractory AML, no patients achieved CR/CRi and OS was only 3.1 months.[53]

Whether the preclinical observation of cross resistance between decitabine, but not azacitidine, and cytarabine is clinically meaningful is not yet known.[54] In general, the available data suggest that HMA might only have limited activity in the setting of relapsed/refractory AML after chemotherapy. Novel salvage therapies within clinical trials are urgently required.

7.4. *Allogeneic Hematopoietic Cell Transplant (HCT)*

Allogeneic HCT is a potentially curative treatment for some patients with AML.[55] Following the introduction of RIC-HCT, an increasing number of elderly patients is offered such a treatment modality.[56–61] Nevertheless, relapse remains an issue.[55] Several studies have shown azacitidine to benefit patients in a post-allogeneic HCT setting as either a maintenance [62–65] or a salvage[64,66–70] therapy. Through an observed expansion of regulatory T-cells, azacitidine might augment the graft-versus-leukemia (GvL) effect without increasing the risk of graft-versus-host disease (GVHD).[71]

7.5. *Quality of Life and Tolerability Considerations*

In a palliative setting, it is essential that a treatment is well tolerated, feasible in an outpatient setting and maintains, or improves, quality of life. Both azacitidine and decitabine have similar safety profiles, which are comparable to that known for LDAC.[11,15,18] The most predominant grade 3/4 AEs are hematological toxicities that are generally manageable by dose delays and/or supportive measures. Pleyer et al. found that the majority of hematological toxicities with azacitidine were documented during early treatment cycles, as is the case in MDS.[25,72] As expected, the most predominant non-hematological toxicities were gastrointestinal events and injection site reactions. These events were generally mild and managed with standard supportive measures.

Furthermore, a recent retrospective analysis indicated that azacitidine can induce transfusion independence in ~50% of previously transfusion-dependent patients with AML.[51] As well as being a strong prognostic factor for prolonged survival, transfusion independence is likely to improve quality of life.[51]

Generally, quality of life must be considered a key goal of treatment. Unfortunately, there is a universal paucity in research evaluating quality of life in both curative and non-curative treatment options in elderly patients with AML. For HMA, patient-reported outcomes were studied in patients with MDS treated with azacitidine. Encouragingly, patients in a phase III study experienced significantly improved quality of life parameters (fatigue, dyspnea, physical functioning, positive affect and psychological distress) than patients receiving BSC.[73] Patient-reported outcomes and quality of life assessments are an important endpoint in the AZA-AML-001 study. Thus, these results will help define the exact impact of azacitidine on the quality of life in elderly patients.

8. Treatment Schedules of Hypomethylating Agents in AML

It is accepted that the treatment schedule of a drug in a phase III study provides guidance to practitioners in treating patients when this agent is approved later. However, this does not necessarily mean that the issue of dosing is finally settled. For HMA, treatment approaches used in clinical trials for patients with AML have largely been extrapolated from the experience in MDS. This is particularly true for decitabine. In the DACO-016 trial, decitabine was applied at a dose of 20 mg/m2/day for 5 days every 4 weeks,[15] Yet, results from a phase II trial with decitabine in elderly patients with AML support the likelihood that a 10 day schedule, with subsequent cycles abbreviated based on response and toxicity could be more effective than the 5 day regimen used in the DACO-016 trial.[19] This issue requires substantiation in prospective clinical trials comparing the two regimens.

9. Differences in Mechanism of Action Between Azacitidine and Decitabine

Phase II data and retrospective studies hint that azacitidine and decitabine may have different activities in some AML populations e.g. WHO–AML (20–30%) and relapsed/refractory AML. Mechanisms of action that might underlie possible differences in clinical activities of azacitidine and decitabine have not been defined; however, preclinical comparisons of the two drugs suggest that they have different activities and are non-equivalent agents.[74]

Based on available data, it is currently unclear whether there is any correlation between the extent of hypomethylation elicited by azacitidine and subsequent clinical response. The evidence from our study [22] and others [75,76] indicate that changes in methylation with azacitidine therapy do not correlate with clinical response. We found that although treatment with azacitidine rapidly reduced LINE-1 DNA methylation levels (a surrogate of global methylation) within the first cycle, it was the initial degree of methylation, rather than treatment-associated changes, which was found to be indicative of subsequent response.[77] Similarly, reduction in the methylation at the $p15^{CDKN2B}$ locus following azacitidine treatment did not correlate with response in patients with MDS. [76] Conversely, a recent phase I study assessing oral azacitidine in patients with MDS,[78] indicated that extent of hypomethylation correlated with response.

Currently, it is also unclear whether response to decitabine correlates with changes in methylation. Some studies suggest that early epigenetic changes predict clinical response in patients with AML treated with decitabine. For example, Yang et al. demonstrated that methylation levels of Alu repeats, LINE-1 and total genomic DNA were significantly decreased within 5 days of treatment with decitabine in patients with AML; reduced methylation correlated with response.[79] Similarly, in a recent study, decitabine-mediated hypomethylation of several tumor-suppressor genes, including $p15^{CDKN2B}$, correlated with subsequent clinical response within the first cycle of treatment.[80] Overall, however, it is not yet clear whether decitabine and azacitidine have different effects on DNA hypomethylation in clinical studies which could reflect functional differences between the two agents.

A key difference between azacitidine and decitabine is that the former, being a ribonucleoside, is incorporated into both RNA and DNA; decitabine, on the other hand, is a deoxyribonucleoside and is only incorporated into DNA.[74] In preclinical studies in mice, it was estimated that 80–90% of azacitidine becomes incorporated into RNA; the remaining 10–20% is incorporated into DNA.[81] In human AML cell lines, approximately 65% of azacitidine appears to incorporate into RNA.[74] Therefore, the conventional description of azacitidine as a DNA hypomethylating agent may be an oversimplification, overlooking potential additional mechanisms of activity mediated via incorporation into newly synthesized RNA, including ribosomal RNA (rRNA), transfer RNA (tRNA), messenger RNA (mRNA) and microRNAs. Studies performed in the 1970s and 1980s demonstrated that azacitidine may alter the processing of tRNAs and rRNAs, leading to inhibition of protein synthesis.[82–84] However, this is a largely understudied area of research. Nevertheless, possibly due to dual effects on DNA hypomethylation and protein synthesis, azacitidine appears to have multiple effects on cells.[74,85,86] In fact, previous studies have indicated that azacitidine rapidly (within 4–8 h) elicits cell death in AML cell lines, and this predominantly occurs during the G-1 phase of the cell cycle (when cells are not actively dividing).[87,88] These observations indicate that the cytotoxic effects of azacitidine are not restricted to actively dividing cells (S phase) and, therefore, may be related to RNA-mediated mechanisms. Decitabine also leads to cell cycle arrest and cell death.[74] However, incorporation of decitabine into DNA is restricted to cells in S-phase (Fig. 3). Azacitidine's potential to kill cells independently of the cell cycle may be important because only a proportion of hematopoietic stem cells in the BM are actively dividing at any given time.[47] Furthermore, RNA-mediated effects on cell viability may occur more rapidly than DNA-mediated effects, which require cell division for passive reduction of DNA methylation to occur. For example, azacitidine-mediated inhibition of protein synthesis in vitro occurred within 24 h in human AML cell lines (which is within the doubling time of these cells).[74] These rapid changes could potentially explain the rapid anti-leukemia activity of azacitidine that has been observed in some trials. [11,22]

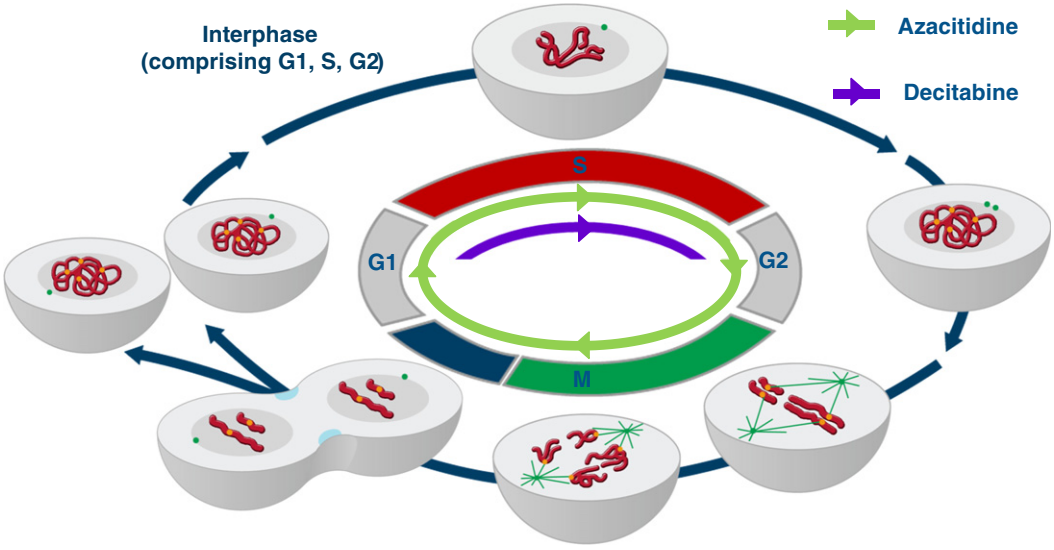

Fig. 3 – Impact of azacitidine and decitabine on the cell cycle. Both incorporate into replicating DNA during the S phase. However, it is thought that azacitidine is also incorporated into RNA which can occur at any stage of the cell cycle. Adapted from Morgan DO. The cell cycle: principles of control. New Science Press, Sunderland, MA; 2007.

Decitabine-mediated re-expression of tumor suppressor genes, such as p15INK4b, takes up to 72 h in culture.[89] Another difference between azacitidine and decitabine is that azacitidine has a greater effect on global gene expression.[74] At this point, it is worth mentioning that several caveats remain to be considered in interpreting these results. The sometimes conflicting data might reflect differences in treatment schedules, loci assessed, the techniques used to quantify methylation and time-points at which samples were taken in relation to treatment. The target cells under investigation represent a further critical point. Most of the studies were conducted on relatively heterogeneous populations of blood or bone marrow cells. Thus, dynamic methylation changes under treatment with HMA at a cellular level could not be distinguished from those occurring at the population level as a result of selective death of cells with a particularly high or low level of methylation.

Finally, the effects of HMA on cell viability cannot be accounted for solely by epigenetic mechanisms. Evidence suggests that a dose-dependent mechanism of action for both HMA exist. The hypomethylation-mediated effect on gene re-expression is demonstrated at low doses while inhibition of cell proliferation (decitabine) and cytotoxicity (azacitidine) is observed at high doses.[74]

Currently, there is no direct clinical evidence to confirm whether differences in mechanism of action translate into differences in clinical activity. This could only be addressed by translational studies and head-to-head prospective trials. However, as the RNA-mediated effects of azacitidine are beginning to be unraveled, specific molecular pathways that underlie possible differences between the two drugs in the clinic are being identified. For example, recent work has demonstrated that azacitidine reduces levels of ribonuclease reductase (RR), a rate-limiting enzyme in DNA synthesis. Although not fully understood, it is thought that this phenomenon may be the result of azacitidine destabilizing the mRNA of one the of RR's subunits. It is possible that this mechanism underlies the activity of the azacitidine in patients with AML. [90] Characterization of differences in the mechanism of action of azacitidine and decitabine at the molecular level may, ultimately, guide treatment decisions in individual patients.

10. Summary and Future Perspectives

Given that the incidence of AML (and indeed secondary AML) increases with age,[91] most patients are deemed unsuitable for, or decline, intensive treatment options,[7] and outcomes following intensive treatment are poor,[6] there is a major unmet medical need for well-tolerated treatment options that can improve survival and quality of life in elderly patients with AML.

Owing to their acceptable tolerability profiles, and emerging evidence of clinical efficacy, HMA may provide an exciting new approach to the treatment of elderly patients, either as monotherapy or in combination regimens with other agents/approaches including histone deacetylase inhibitors, immunomodulatory drugs like lenalidomide, cytotoxics or allogeneic HCT. In the European Union (EU), the recent approval of decitabine for the treatment of elderly patients (≥65 years old) with AML will certainly provide a much needed treatment option for patients who are not candidates for IC. However, the phase III DACO-016 data need to be interpreted with caution, given that the trial did not achieve its primary endpoint and it was not designed as a non-inferiority trial. On the other hand, concerns regarding the efficacy of decitabine are, in part, mitigated by its favorable tolerability profile and the dearth of other treatment options in this setting.

Clinical evidence demonstrates that azacitidine has promising activity in patients with AML. It is already licensed for patients with 20–30% blasts (for whom it confers a survival benefit) [11] and phase II data/retrospective studies suggest that it is active and well tolerated in patients with >30% BM blasts,[22] including those with relapsed/refractory AML.[22,41,51] Furthermore, azacitidine appears to prolong survival in patients with AML without the achievement of CR.[22] Owing to these findings, data from the AZA-AML-001 trial are eagerly awaited to define the role of azacitidine in the treatment of AML in the elderly.

How does the accumulating evidence of the clinical activity of HMA change the treatment landscape for elderly patients with AML? Indeed, these developments do not render intensive treatment options obsolete. The previously discussed survival data and limitations of HMA must be considered carefully (the DACO-016 study did not meet its primary end point of improved survival with decitabine and the results of the phase III AZA-AML-001 trial are yet unavailable).

Thus, wherever possible, both curative and non-curative treatment options should be offered within clinical trials. If this is not feasible, patients and care-givers need to be made absolutely clear of the risk–benefit profiles of (where applicable) IC, LDAC, HCT and HMA. Evidence suggests that elderly patients often confuse curative and non-curative approaches, highlighting the need for thorough counseling between physician and patient, so that the latter can make an informed choice on their preferable approach. [9]

Therefore, before embarking on a HMA-based treatment regimen, it is essential that goals of therapy are clearly elucidated. Both patient- and disease-related prognostic factors that may indicate, or preclude, IC or LDAC such as age, comorbidity burden, PS, cytogenetics and likelihood of CR need to be considered in decision making.[8,32–35] Furthermore, recent developments suggest that molecular profiling of aberrations such as *NPM1* and *DNMT3A* mutations, and *MLL* translocations, could identify patients who are most likely to benefit from a certain treatment or dose intensity.[92–94] Our approach is to discuss in depth with the patients the possibilities available. We suggest a curative treatment option (IC and/or HCT) in patients with no contraindications or a non-curative approach within a trial. If clinical studies are not feasible and based on our experience, we recommend azacitidine in patients with BM blasts 20–30%. If blasts are >30%, we advice either LDAC or decitabine based on cytogenetics. We must reiterate that there are no direct head-to-head data available at the moment to make objective comparisons between azacitidine and decitabine. Nevertheless, it may well be that further molecular and translational studies, aimed at fully understanding the mechanism of action of the two drugs, could drive treatment choices in specific subgroups of patients.

One additional perspective merits mentioning. HMA and IC are not necessarily mutually exclusive. Indeed, in vitro data suggest a possible synergistic effect of cytarabine and azacitidine when azacitidine is administered before cytarabine probably through the induction of deoxycytidine kinase by azacitidine which phosphorylates cytarabine to its active compound, ara-CTP.[95,96] Yet, clinical data to the safety, efficacy, and optimal scheduling of HMA and chemotherapy in acute leukemias are very limited. In 17 pediatric patients with relapsed acute lymphoblastic leukemia after high-dose cytarabine, treatment with azacitidine followed by another course of high-dose cytarabine yielded a complete remission in two of 9 evaluable patients in a phase I-study. [97] Recently, a pilot trial in elderly patients with newly diagnosed AML which assessed the safety of azacitidine added to standard induction and consolidation therapy was published. The authors concluded that the combination of azacitidine 75 mg/m^2 with standard induction therapy was feasible and this combination selected as an investigational arm in a randomized phase-II study, which is currently halted due to an increased cardiac toxicity in the experimental arm.[98] Another clinical trial is evaluating an initial priming with azacitidine and a sequential, response-adapted application of induction chemotherapy in elderly patients with AML (DRKS00004519). Thus, integrating both options in well-designed trials might further optimize outcome even in younger patients.

In summary, there is strong preclinical rationale, and clinical data, to support the use of HMA in elderly patients with AML. The AZA-AML-001 trial will be instrumental in indicating azacitidine's role in this setting and will determine whether it can provide an additional option to decitabine in this area of unmet medical need.

Disclosures and Conflict of Interest Statements

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