How and when to decide between epigenetic therapy and chemotherapy in patients with AML

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Remission induction with chemotherapy has long been the frontline treatment of acute myeloid leukemia (AML). However, intensive therapy is limited in frail patients by its associated toxicity and higher rates of failure or relapse in patients with chemoresistant disease, such as secondary AML or poor-risk cytogenetics. Frailty and chemoresistance are more frequent in older adults with AML. In recent years, epigenetic therapies with the hypomethylating agents decitabine and azacitidine have been thoroughly explored in AML. The results of two pivotal studies carried out with these agents in older adults with newly diagnosed AML have challenged the role of intensive chemotherapy as the frontline treatment option in this high-risk population. Here, we review the results of treatment with intensive chemotherapy and hypomethylating agents in older patients with AML; discuss the patient- and disease-specific criteria to integrate into treatment decision making; and also, highlight the methodological limitations of cross-study comparison in this population.

Learning Objectives

- To learn the modalities, clinical results, and limitations of intensive chemotherapy and hypomethylating agents as frontline treatment in patients with AML
- To learn the patient- and disease-specific criteria that must be integrated into the individualized therapeutic decision in high-risk AML

Introduction

Currently, treatment decision making in patients with newly diagnosed acute myeloid leukemia (AML) is a stepwise process. Early diagnosis is critical for the minority of patients with acute promyelocytic leukemia, for whom long-term cure may be achieved using specific therapy based on retinoic acid and arsenic trioxide. The overall approach is that AML cytogenetics and genomics are then determined as precisely as possible to assess individual prognosis; orient risk-adapted therapeutic strategies, notably allogeneic hematopoietic stem cell transplantation (HSCT) in first remission; and enroll patients with specific molecular targets (*FLT3* and *IDH1/2* mutations) into dedicated clinical trials evaluating new targeted agents.[1] Patients' general health status is also concomitantly evaluated, and potential comorbidities are explored for each patient to adjust treatment intensity to the patient's ability to cope with treatment-associated toxicities dominated by myelosuppression and cardiotoxicity. In older patients, a population that is generally defined as patients older than 60 to 65 years old, estimating benefit/risk associated with treatments of various intensities is of utmost importance.

The poor prognosis of older adults with AML is an intricate consequence of patient-related factors (such as comorbidities) and disease-related chemoresistance (notably because of more frequent secondary AML), both of which can be seen, albeit at lower frequencies, in adults below the age of 60 years old. In patients over the age of 60 years old, except in those with very proliferative disease, delaying AML treatment does not seem to affect prognosis.[2,3] In older patients, such as in those with relapsed/refractory (R/R) AML, the choice between an intensive chemotherapy (ICT) regimen or a lower-intensity treatment is crucial, because these two options are not associated with equivalent outcomes, at least in the short term. To date, lower-intensity AML therapy is mostly represented by epigenetic therapy, initially developed for patients with higher-risk myelodysplastic syndrome (MDS). Both hypomethylating agents (HMAs) decitabine (DAC) and azacitidine (AZA) have shown their ability to improve median and short-term overall survival (OS) compared with low-dose cytarabine (LDAC) or best supportive care (BSC) only, even if this has not translated into improved cure rates. In this review, we will discuss how and when to decide between HMAs and ICT, focusing on older patients with AML.

Standard chemotherapy

In older patients with AML, standard ICT allows 45% to 65% of older adults with newly diagnosed AML to achieve a complete remission (CR). Overall, because of worse tolerance of ICT and higher intrinsic AML resistance, median OS does not usually exceed

Conflict-of-interest disclosure: H.D. is on the Board of Directors or an advisory committee for Menarini, Servier, Seattle Genetics, Cellectis, Janssen, Astellas, Karyopharm, Sunesis, Daiichi Sankyo, Agios, Kite Pharma, Jazz Pharmaceuticals, Novartis, Incyte, Pfizer, Amgen, and Celgene; has received research funding from Servier, Kite Pharma, Jazz Pharmaceuticals, Incyte, Pfizer, and Amgen; has consulted for Menarini, Jazz Pharmaceuticals, Celgene, Chugai Pharmaceutical Co., and Roche; has received honoraria from Menarini, Servier, Seattle Genetics, Cellectis, Janssen, Astellas, Karyopharm, Sunesis, Daiichi Sankyo, Agios, Kite Pharma, Jazz Pharmaceuticals, Novartis, Incyte, Pfizer, Amgen, and Celgene; and has been affilitated with the Speaker's Bureau for Incyte, Pfizer, Amgen, and Celgene. R.I. has received research funding from Janssen and honoraria from Celgene.

Off-label drug use: None disclosed.

12 to 18 months, and 5-year OS remains <15%. Standard induction chemotherapy is a combination of intermediate-dose cytarabine and an anthracycline administered for 7 and 3 days (7 + 3), respectively. Cytarabine is given as continuous IV infusion at the daily dose of 100 or 200 mg/m^2 per day. The anthracycline can be either daunorubicin or idarubicin, usually given at 60 and 12 mg/m^2 per day, respectively, with a reduced dose of 45 mg/m^2 per day daunorubicin being considered suboptimal.[4] It has been reported that idarubicin might be associated with more rapid CR achievement and a higher cure rate in the long term.[5] Despite progress made in terms of supportive measures, notably in antibiotic and antifungal therapy, early mortality remains high. Early death in induction occurs before response evaluation in ~10% to 20% of patients selected to receive ICT, and the 60-day mortality rate ranges from 15% to 30%. After CR has been achieved, it is acknowledged that, in patients capable of tolerating additional chemotherapy, it is preferable to administer some form of postremission therapy, although there is no standard consolidation or maintenance regimen.

Prospective randomized studies comparing different postremission chemotherapy regimens are sparse. In the Cancer and Leukemia Group B (CALGB) 8525 Study, which compared three different dose-intensity schedules of cytarabine, older patients did not benefit from dose intensification.[6] In the CALGB 8923 Study, addition of two intensive consolidation courses with intermediate-dose cytarabine and mitoxantrone yielded similar survival as four LDAC courses.[7] Moreover, in the Acute Leukemia French Association (ALFA) 9803 Study, six outpatient mild-intensity postremission courses yielded superior survival compared with one intensive consolidation course.[8] In addition, no survival advantage was observed in patients ages 65 to 70 years old who received two intensive consolidation courses rather than one single intensive consolidation course in the concomitant ALFA 9801 Trial.[9] Finally, in the German AML Intergroup Study, which randomized older patients between one common standard arm and two other chemotherapy strategies used by distinct German cooperative groups, no differences in relapse-free and OS were observed.[10] As in younger adults, allogeneic HSCT is considered to be probably the best option to prevent AML recurrence in selected patients with intermediate- or adverse-risk AML, even if no formal evidence for this assertion has been provided to date. While awaiting the results of an ongoing European randomized trial (NCT00766779) that is prospectively comparing reduced-intensity conditioning (RIC) transplantation with additional chemotherapy, with OS as the primary end point, HSCT is offered to an increasing proportion of older patients in first remission. The best therapy before HSCT in this population has been an open issue for years.

Drugs that could potentially improve outcome over current ICT in the near future include the antibody-drug conjugate (ADC) gemtuzumab ozogamicin and the liposomal CPX-351 chemotherapy as well as FLT3 and IDH1/2 inhibitors.[11,12] A recent French study also suggested that the addition of norethandrolone during postremission chemotherapy may improve long-term outcome.[13] The rationale for this latter study is based on the potential ability of androgens to block proliferation and induce differentiation of AML cells.

Genetic factors with prognostic impact

In intensively treated AML patients, pretreatment prognostic factors are usually separated into two groups: AML-related genetic factors governing the risk of AML resistance or recurrence and patient-related factors governing the risk of treatment-associated toxicity and mortality. The former are much better standardized than the latter.

Table 1. European LeukemiaNet risk stratification by genetics

Risk category	Genetic abnormality
Favorable	t(8,21)(q22,q22.1), *RUNX1-RUNX1T1*
Favorable	inv(16)(p13.1q22) or t(16,16)(p13.1,q22), *CBFB-MYH11*
Favorable	Mutated *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}*
Favorable	Biallelic mutated *CEBPA*
Intermediate	Mutated *NPM1* and *FLT3*-ITD^{high}*
Intermediate	Wild-type *NPM1* without *FLT3*-ITD or with *FLT3*-ITD^{low}* (without adverse-risk genetic lesions)
Intermediate	t(9,11)(p21.3,q23.3), *MLLT3-KMT2A*†
Intermediate	Cytogenetic abnormalities not classified as favorable or adverse
Adverse	t(6,9)(p23,q34.1), *DEK-NUP214*
Adverse	t(v,11q23.3), *KMT2A* rearranged
Adverse	t(9,22)(q34.1,q11.2), *BCR-ABL1*
Adverse	inv(3)(q21.3q26.2) or t(3,3)(q21.3,q26.2), *GATA2, MECOM(EVI1)*
Adverse	−5 or del(5q), −7, −17/abn(17p)
Adverse	Complex karyotype,‡ monosomal karyotype§
Adverse	Wild-type *NPM1* and *FLT3*-ITD$^{high(a)}$
Adverse	Mutated *RUNX1*‖
Adverse	Mutated *ASXL1*‖
Adverse	Mutated *TP53*¶

ITD, internal tandem duplication.

*Low indicates low allelic ratio (<0.5), high indicates high allelic ratio (>0.5), and semiquantitative assessment of *FLT3*-ITD allelic ratio (using DNA fragment analysis) is determined as the ratio of the area under the curve *FLT3*-ITD divided by the area under the curve *FLT3*-wild type.

†The presence of t(9,11)(p21.3,q23.3) takes precedence over rare, concurrent adverse-risk gene mutations.

‡Three or more unrelated chromosome abnormalities in the absence of one of the WHO-designated recurring translocations or inversions [ie, t(8,21), inv(16); t(16,16), t(9,11), t(v,11)(v,q23.3), t(6,9), inv(3); or t(3,3), AML with *BCR-ABL1*].

§Defined by the presence of one single monosomy (excluding loss of X or Y) in association with at least one additional monosomy or structural chromosome abnormality (excluding core binding factor AML).

‖These markers should not be used as an adverse prognostic marker if they cooccur with favorable-risk AML subtypes.

¶*TP53* mutations are significantly associated with AML with complex and monosomal karyotypes.

As summarized in the recently updated recommendations of the European LeukemiaNet panel,[1] cytogenetics and molecular genetics allow classification of AML cases into the three categories: favorable, intermediate, and adverse risk (Table 1). Among the adverse-risk subset, particularly worrisome are AML with a monosomal karyotype, *TP53* gene mutation, and abnormalities involving the *MECOM* (*EVI1*) gene. Importantly, the better outcome associated with entities considered as favorable per European LeukemiaNet criteria (Table 1) has been validated in older patients treated intensively and translates into higher cure rates.[5,14,15] More recently, the complexity and prognostic significance of individual gene mutation patterns as revealed by next generation sequencing has been specifically explored in older patients. Early studies confirmed the favorable impact of *NPM1* mutations. However, the presence of *FLT3* internal tandem duplication and *TP53* mutations was associated with shorter OS. Interestingly, some driver gene mutations, such as *DNA-methyltransferase 3A* (*DNMT3A*), *TET2*, *SRSF2*, and *ASXL1*, may be detected in seemingly healthy patients before overt AML development.[16,17] Such preexisting, MDS-like[18] clonal hematopoiesis is more frequent in older patients, and the persistence of preleukemic clones during CR seems to represent a poor prognostic factor associated with higher relapse incidence in these patients.[19] A mutation signature mostly including spliceosome and cohesion genes

has been proposed to define secondary AML. Although this signature does not impart poor prognosis compared with de novo AML,[20] additional work is required to determine whether these molecularly defined secondary AML patients benefit from epigenetic therapy. In a sense, these novel observations enlarge the field of AML secondary to a prior MDS, a setting reported as being of poor prognosis for years. Finally, a so-called leukemic stem cell gene expression signature, which is more frequently observed in AML with an adverse karyotype but can also be seen in the intermediate-risk subset, has been recently shown to be associated with poor outcomes.[21]

Assessment of eligibility for standard induction therapy

Except for very old patients over the age of 80 to 85 years old, chronologic age alone is not a good criterion for fitness assessment. Beyond subjective physical function scales, such as Eastern Cooperative Oncology Group (ECOG) performance status (PS), there is, however, no consensus definition of patients unfit for intensive therapy. Although PS is a good tool to detect frail patients, it does not detect subclinical impairments that could make a patient more vulnerable to therapy.[22] Interestingly, poor PS is significantly associated with higher white blood cell count (WBC) at diagnosis, suggesting that PS at diagnosis captures both the patients' durable intrinsic frailty and transient disease–related vulnerability. Geriatric assessment may be of help but is limited to studies of small sample size to date, maybe because of the very small proportion of patients over the age of 80 to 85 years old in most current older AML intensive trials. In current practice, eligibility for ICT is mostly defined in clinical trials on the basis of PS and specific markers for cardiac, renal, and liver functions, which incidentally, do not always represent formal contraindications for ICT.[23] Comorbidity burden measurement using, for instance, the Charlson Comorbidity Index or the Hematopoietic Cell Transplantation Comorbidity Index[24] tends to be more frequently prospectively evaluated. Several scores mixing disease-related and patient-related factors have been developed but are rarely used prospectively.[25] In the real-life setting (ie, outside of clinical trials), treatment intensity mostly relies on the physician's subjective assessment of a patient's vulnerability and expectations, which may frequently differ from the patient's viewpoint.[26] A direct consequence of this lack of standardization is the extreme difficulty of capturing the extent to which a trial's study population has been truly selected and thus, comparing one study with another. This remains a major concern for evidence-based treatment decision-making recommendations between ICT and lower-intensity therapy in AML patients.

Epigenetic therapy

The role of epigenetic deregulation in the pathogenesis of AML has been a matter of intense research during recent years. As mentioned above, recurrent somatic mutations in key genes involved in the epigenetic machinery (*DNMT3A*, *TET2*, *IDH1*, *IDH2*, and *ASXL1*), also present in MDS, have been identified in AML and preleukemic clones. Although aberrant methylation in AML goes beyond the role of these mutations,[27] therapies targeting DNMTs have been investigated in MDS and AML. Both DAC and AZA are pyrimidine analogs acting as DNMT inhibitors, leading to global hypomethylation of cytosine residues at not only cytosine guanine dinucleotide–rich gene promoters but also, distal enhancers critical for gene expression regulation.[28] More recently, an oral formulation of AZA (CC-486) and a second generation HMA, guadecitabine (SGI-110),[29] have entered clinical development.

Prospective studies evaluating DAC or AZA in AML patients are summarized in Table 2.[30-38] These studies focused on either World Health Organization (WHO) AML patients or MDS patients, including WHO AML patients with 20% to 30% bone marrow (BM) blasts. In these studies, AZA was generally administered subcutaneously according to the MDS schedule (75 mg/m^2 per day for 7 days per cycle), whereas DAC was administered IV according to different dose schedules. Initially, DAC was given at 15 mg/m^2 per 8 hours IV for 3 days every 6 weeks.[35,37] An alternative outpatient dose schedule (20 mg/m^2 per day for 5 days every 4 weeks) was also developed.[32,36] An even more prolonged 10-day administration schedule has been proposed as potentially associated with a higher response rate.[33] With the exception of the most recent AZA-AML-001 Study phase 3 trial, AML studies recruited patients considered unsuitable for standard intensive AML therapy. Median ages were thus relatively high, ranging from 65 to 75 years old. With HMAs, the best hematologic responses are frequently reached after a median of two to four cycles and may even be observed later with continuous therapy in patients classified early with only stable disease. Continuous HMA administration is thus recommended until disease progression or limiting toxicities, the latter being relatively rare, because these agents are, in general, well tolerated. Such a strategy is clearly at odds with standard ICT. This potential ability of HMAs to prolong survival, despite the lack of remission achievement through the maintenance of stable diseases and/or improvement of cytopenias, represents a novel paradigm in AML therapy.[39,40] These differences in HMA vs chemotherapy explain why OS must remain the primary end point when trying to compare the two strategies, although OS might be influenced by subsequent uncontrolled crossovers, HSCT, or enrolment in other investigational trials.

To date, the two largest HMA studies are randomized phase 3 studies of HMA vs patient/physician choice among various conventional care regimen (CCR) options.[36,38] The DACO-16 Study compared DAC with LDAC or BSC, whereas the AZA-AML-001 Study compared AZA with LDAC, BSC, or ICT. Eligibility criteria were not identical in the two studies, with more proliferative disease allowed in the DAC trial.[41] In addition, the LDAC dose schedule differed: 20 mg/m^2 per day for 10 days every 4 weeks in the DAC study and 20 mg twice per day for 10 days every 4 weeks in the AZA study. Both studies showed significant improvement in median OS in the HMA arm (7.7 months with DAC and 10.4 months with AZA) compared with the CCR arm (5.0 months in the DAC study and 6.5 months in the AZA study). However, because of the convergence of survival curves in the longer term, cure rates were not improved by HMA therapy. Rates of CR and CR + CR with incomplete blood count recovery were 15.7% and 25.6% with DAC, respectively; 19.5% and 27.8% with AZA, respectively; 7.9% and 10.7% with LDAC in the DACO-16 Study, respectively; and 24.1% and 25.9% with LDAC in the AZA-AML-001 Study, respectively. Because these trials were designed to compare HMA with CCR as a whole, it is difficult to extrapolate the results in any specific CCR subgroup analysis. It seemed, nevertheless, that clinically meaningful gains in median OS were still observed when comparing either DAC or AZA with LDAC. In addition, in the AZA-AML-001 Study, AZA therapy was associated with lower incidence rates of treatment-emergent anemia, neutropenia, febrile neutropenia, and thrombocytopenia compared with LDAC.[38] Real-life studies of AZA therapy in patients with previously untreated or R/R AML are summarized in Table 3.[42-51] Overall, these real-life data, collected through national/regional registries or compassionate use programs, confirm that the outcome described in AZA trials could be reproduced in fewer selected patients and across different AML subtypes.

Clinical parameters as predictors of HMA response

Significant HMA activity has been observed across most AML subgroups, including those with intermediate- or adverse-risk

Table 2. Prospective DAC or AZA studies in AML patients

Reference	AML type	Median age (range), y	Drug dose and schedule	Patients, *N*	CR/PR (%)	ORR* (%)	Median OS, mo
31							
CALGB 8421	AML (20%-30% BM blasts)	65 (35-81)	AZA 75 mg/m^2 per day for 7 d, IV	25	4 (12)	12 (48)	—
CALG 8921	AML (20%-30% BM blasts)	66 (23-82)	AZA 75 mg/m^2 per day for 7 d, SC	26	3 (12)	9 (35)	—
CALGB 9221	AML (20%-30% BM blasts)	69 (1-82)	Two randomization arms				
			AZA 75 mg/m^2 per day for 7 d, SC	27	2 (7)	10 (37%)	19.3
			BSC	25†	0	2 (8)†	12.9
32	WHO-AML	74 (61-87)	DAC 20 mg/m^2 per day for 5 d, IV	55	13 (24)‡	14 (25)	7.7
33	WHO-AML	74 (60-85)	DAC 20 mg/m^2 per day for 10 d, IV	53	25 (47)‡	34 (64)	12.6
34	AML (20%-30% BM blasts)	70 (62-80)	Two randomization arms				
			AZA 75 mg/m^2 per day for 7 d, SC	55	10 (18)‡	—	24.5
			BSC, LDAC, or ICT	58	9 (16)‡	—	16
35	WHO-AML	72 (56-86)	DAC 15 mg/m^2 per 8 hours for 3 d, IV	227	59 (26)§	—	5.5
36	WHO-AML	73 (64-91)	Two randomization arms				
			DAC 20 mg/m^2 per day for 5 d, IV	242	44 (18)	73 (30)	7.7
			BSC or LDAC	243	27 (11)	34 (14)	5
37	AML (20%-30% BM blasts)	69.5 (61-90)	Two randomization arms				
			DAC 15 mg/m^2 per 8 hours for 3 d, IV	40	6 (15)	12 (30)	8
			BSC	35	0	0	6
38	WHO-AML‖	75 (64-91)	Two randomization arms				
			AZA, 75 mg/m^2 per day for 7 d, SC	231	50 (22)	70 (30)	10.4
			BSC, LDAC, or ICT	247	57 (23)	65 (26)	6.5

ORR, overall response rate; PR, partial remission; SC, subcutaneous.

*ORR including CR/PR, CR with incomplete blood count recovery, and/or hematologic improvements.

†Thirteen patients received study drug after crossover.

‡CR only.

§PR criteria were used in this study, and it included patients with persistent cytopenia.

‖If >30% marrow blasts and WBC < 15 G/L.

Table 3. Real-life studies with AZA in AML patients

Reference	Drug	Patients, *N*	AML type	Prior AML therapy	Median age (range), y	Median OS, mo
42	AZA	54	Post-MPN AML (48%) or MDS	None	69.5 (37-89)	8*
43	AZA	82	Any WHO-AML subtype	57%	72 (29-87)	9
44	AZA ± VPA or ATRA	149	Any WHO-AML subtype	None	74 (31-91)	9.4
45	AZA	302	Any WHO-AML subtype	54%	73 (30-93)	9.6
46	AZA	95	Any WHO-AML subtype	None	76 (71-81)	11.3
47						
Training set	AZA	110	Any WHO-AML subtype	None	75 (56-89)	8.1
Validation set	AZA	261	Any WHO-AML subtype	None	75 (31-93)	10.0
48	AZA	95	WHO-AML†	None	77 (23-93)	10.8
49	AZA	107	Post-MDS, post-MPN, and therapy-related AML	None	76.5 (71-81)	10.8
50	AZA	47	Any WHO-AML subtype	All R/R AML	63 (29-79)	9
51	AZA ± VPA or ATRA	130	Any WHO-AML subtype	All R/R AML	67 (50-80)	8.4

ATRA, all-trans retinoic acid; MPN, myeloproliferative neoplasm; VPA, valproic acid.
*In patients fulfilling WHO-AML diagnostic criteria.
†With >30% marrow blasts and WBC < 15 G/L (AZA-AML-001 Study entry criteria).

cytogenetics, >30% or 50% BM blasts, post-MDS AML, or AML with myelodysplastic-related changes as defined by the WHO. Although adverse-risk genetics remains a poor prognostic factor in patients receiving frontline HMA therapy,[42,45-48] greater benefits have been associated with AZA therapy in patients with poor-prognostic karyotypes and/or WHO myelodysplastic-related changes AML in the comparative AZA-AML-001 Study (John F. Seymour, Hartmut Döhner, Aleksandra Butrym, et al, manuscript submitted, 2017).[52] AZA has also been reported as a relevant frontline option in patients with AML or MDS with chromosome 3q abnormalities.[53] Probably because of preferential selection of older patients, the prognostic impact of age in HMA studies remains unclear. Age was not significantly associated with OS in a multivariate analysis of outcomes in some AZA real-life cohorts[44,45] but not in all.[46] Age was, however, significantly associated with OS of the whole population of the DAC vs treatment choice trial[54] but not in the AZA-AML-001 Study.[38] As with intensive therapy of AML, an ECOG PS higher than two remains of strong prognostic value when older AML patients are treated front line with HMAs.[44,45,47,48] The prognostic value of WBC at diagnosis remains uncertain but was associated with worse long-term outcome in the DACO-16 Study and most real-life AZA reports. Because of their mechanisms of action, HMAs are generally not considered as a good frontline option in high WBC patients with rapidly proliferative AML.[44-47,51,54] Based on previous observations by Gardin et al,[55] 15×10^9/L was retained as the upper WBC limit for eligibility in the AZA-AML-001 Study.

Genetic predictors of HMA response

The precise mechanisms of action of HMAs remain unclear at both the molecular level, where reexpression of tumor suppressor genes on HMA exposure has long been sought without success,[56] and the cellular level, where it is increasingly apparent that HMAs do not allow clonal eradication,[57] although transient clonal reduction has been reported.[58] As a consequence, validated biomarkers of HMA activity are yet to emerge. A number of reports have investigated the predictive and prognostic role of gene mutations in AML and MDS treated with HMAs. Results were limited by the small size of most cohorts and their retrospective nature. Convergent results nevertheless suggest that mutations in epigenetic regulators, such as *TET2* or *DNMT3A*, could predict a superior response rate, although this does not translate into a survival benefit.[59-62] More recently, in a series of 116 patients with AML or MDS treated with 10-day courses of DAC, higher response rates were observed in patients with adverse-risk cytogenetics and/or *TP53* gene mutations compared with other patients. This improved response rate also did not translate into a survival benefit.[58] The favorable role of *TP53* mutations has not been observed in other cohorts of AML patients treated with HMA at conventional and thus, less intensive schedules.[63] These observations raise the intriguing possibility that specific HMAs and schedules may differently affect leukemic clones and warrant additional prospective validation given the poor prognosis of this patient population, even after allogeneic transplant. Finally, in the AZA-AML-001 Study, patients with *TP53* and/or *NRAS* gene mutation treated with AZA had longer OS than similar patients treated with CCR, whereas OS was similar in both the AZA and CCR arms for patients with a mutation in any of the *DNMT3A*, *IDH1/2*, or *TET2* genes.[64] In the same study, *FLT3* gene mutations had a negative impact on OS in patients treated with AZA but did not have a negative impact on those in the CCR arm.

Methylation changes as a predictor of HMA response

Global hypomethylation has been consistently reported after in vitro and in vivo exposure to HMAs in MDS or AML,[65,66] and some reports have suggested more profound hypomethylation in responders.[29,57] Several studies have reported reversal of methylation or gene reexpression at specific loci on HMA treatment[33,67,68]; however, few reports have identified patterns of methylation at baseline that could predict response and/or survival of patients treated with HMA.[69,70] This likely reflects the technical limitations of older methylome strategies focusing on gene promoter cytosine guanine dinucleotide islands[69] as well the intratumoral heterogeneity of methylation patterns in AML.[71] The heterogeneity of patients analyzed and the early analysis of posttreatment methylation changes, not to mention the uncertainties regarding the most relevant mechanisms of actions of these drugs in AML, may also explain the limited role of methylation studies in predicting HMA activity. Authors have also evaluated the expression or polymorphisms in genes involved in the metabolism of HMA, including the transporter hENT1, or the enzymes uridine cytidine kinase, deoxycytidine kinase, and cytidine deaminase, without reproducible results.[69,72] Taken together, identification of relevant biomarkers guiding the allocation of HMA in AML will require a better understanding of the target cells and the mechanism of action of these drugs that can also act in a noncellular intrinsic manner on the immune response.

Given the significant unmet need, current developments of almost all new antileukemic agents include combination trials with AZA, DAC, or even LDAC in patients with newly diagnosed or R/R AML

Table 4. Deciding between chemotherapy and epigenetic therapy in patients with AML

Factors in favor of ICT	Factors in favor of epigenetic therapy
Age <70 y	Age ≥80 y
ECOG PS < 2	ECOG PS ≥ 2
Low CCI, HCT-CI (<3)	High CCI, HCT-CI (≥3)
Higher WBC*	Lower WBC*
De novo AML	Secondary AML (post-MDS, post-MPN)
AML not classified as WHO MRC-AML	AML classified as WHO MRC-AML
Favorable genetics: favorable ELN category (Table 1)	Unfavorable genetics: monosomy 5 or 7, del(5q); complex, monosomal karyotype; *TP53* gene mutation
FLT3-ITD	No *FLT3*-ITD
No epigenetic gene mutation?	Epigenetic gene mutations (*TET2*, *DNMT3A*)?

CCI, Charlson Comorbidity Index; ELN, European LeukemiaNet; HCT-CI, Hematopoietic Cell Transplantation Comorbidity Index; ITD, internal tandem duplication; MPN, myeloproliferative neoplasm; MRC, myelodysplastic-related change.
*Higher WBC is associated with a worse prognosis after ICT; nevertheless, the prognosis of patients with WBC > 15 000 G^9/L might be even worse after HMA therapy, at least when treated with AZA[55] and maybe less when treated with DAC.[41]

deemed unfit for ICT. Early results have been reported with agents, such as the kinase inhibitors sorafenib and midostaurin, BCL2 inhibitor venetoclax, MDM2 inhibitor idasanutlin, or SMO inhibitor glasdegib, or even with chemotherapeutic agents or ADCs, such as vosaroxin, gemtuzumab ozogamicin, or vadastuximab talirine. Combining HMAs with histone deacetylase inhibitors, another class of epigenetic drugs, has yielded disappointing results to date. Studies with new antibodies, ADCs, immune checkpoint inhibitors, or other epigenetic agents similar to IDH inhibitors are ongoing. Unfortunately, the efficacy of such combinations is too frequently hindered by their poor tolerance in older unfit patients, raising the issue of their evaluation in fitter patients, potentially against ICT.

How to decide between chemotherapy and HMAs?

The two treatment options described above, ICT and epigenetic therapy, are very different by nature. Intensive therapy systematically induces transient but prolonged myelosuppression requiring hospitalization because of worsening neutropenia and thrombocytopenia, with a risk of infections and/or hemorrhages that may be associated with a higher early mortality rate. However, the CR rate is higher after ICT than after HMA therapy, potentially offering a better quality of life to those patients who may reach CR, at least until eventual AML recurrence. Epigenetic therapy is less toxic, may be administered in the outpatient setting, and might thus be associated with a better quality of life during therapy and lower early mortality rate. The CR rate is significantly lower than after ICT, but HMAs seem to be capable of maintaining stable diseases or incomplete responses, leading to a median OS that might eventually be similar to that observed after ICT.

Summarizing this, HMAs could represent an option retained by default in patients "unlikely to benefit from ICT" as defined by their physicians through a global evaluation based on age, ECOG PS, fitness assessment, history of prior hematologic disorders or chemotherapy, WBC, AML genetic feature, comorbidities, and polypharmacy. This is, in fact, what happens in real life. According to real-life reports and one recent population-based study from the United States,[46,49,55,73-75] it can be estimated that approximately one-half of all older patients treated for AML receive HMA, whereas one-half receive ICT, with variations in proportions according to countries and centers. In these reports, patient characteristics differed markedly between the HMA and ICT cohorts, underlying major and reproducible selection biases. Patients treated with HMAs were significantly older, had fewer comorbid diseases, had more frequent secondary AML, had lower WBC and/or BM blast percentage at diagnosis, and had higher rates of adverse-risk karyotypes. Resulting observations were similar early mortality rates in HMA vs ICT cohorts[46,55,73,74] and longer OS in ICT vs HMA in some cohorts,[46,73] but these retrospective comparisons were clearly confounded by patient selection issues. To address this problem, two French groups performed propensity score matching analyses, which identified 63 and 66 pairs of higher-risk patients, in whom OS was ultimately similar after ICT or AZA therapy.[46,55] To date, no large randomized studies have been initiated aiming to compare epigenetic therapy with ICT in older AML patients, and any such study would probably face major recruitment and/or selection problems. ICT was offered as a CCR option in the randomized phase 3 AZA-AML-001 Study. However, most patients in the CCR arm received LDAC, and only a minority of the whole study population was randomized between AZA and ICT. There were thus not enough patients to make any definitive statements about the relative benefit of AZA and chemotherapy in patients who were deemed ICT candidates. The lower than expected rate of patients randomized against ICT in the study (18% when 50% could have been anticipated) shows how the experimental AZA arm skewed the study population in this trial, which does not encompass the full spectrum of older patients with AML.

In conclusion, there is definitely a subgroup of poor-risk AML patients in whom epigenetic therapy may yield similar or maybe even better outcomes than chemotherapy. This subgroup cannot be readily defined today by universal standardized criteria, because final decisions are highly individualized, taking into account balanced benefit/risk as well as subjective assessments, not to mention the patients' opinion. Factors that could be used to guide the individual treatment decision are summarized in Table 4.

Some important open issues

High WBC AML

How to manage older AML patients with high WBC at diagnosis remains an open issue, because these patients appear to poorly respond to both chemotherapy and HMAs. Because they frequently present activating kinase mutations, such as *FLT3* internal tandem duplications, combination with kinase inhibitors represents an interesting approach.

Secondary AML in patients previously treated with HMAs

A proportion of higher-risk MDS patients failing HMA quickly progress to secondary AML. The outcome of higher-risk MDS patients after failure of HMAs is dismal, with a median OS around 3 months,[76] and there are no approved second-line regimens. Notably, ICT[77] or administration of other first generation HMAs seems of limited efficacy in this context,[78] although newer HMAs, such as guadecitabine, seem to retain some activity in this setting.[29] Of note, guadecitabine is

currently prospectively under evaluation vs treatment of choice (LDAC, AZA, and DAC) in the frontline setting (NCT02920008).

Allogeneic HSCT after HMA vs ICT

Several retrospective studies have reported comparable outcome of higher-risk MDS patients who received allogeneic HSCT after ICT or HMA.[79] These reports were likely biased because of their retrospective nature. A recent prospective Italian trial showed the feasibility of HSCT in the majority (74%) of higher-risk MDS or AML patients with a donor who were treated with AZA.[80] This figure compares favorably with a previous prospective report with ICT as a frontline option, where only a minority (7%) of patients ultimately received HSCT,[81] although the latter included patients with much higher-risk disease, and both RIC availability and supportive care have made significant progress in the decade separating these two reports. The European Organization for Research and Treatment of Cancer (EORTC) is currently conducting a prospective randomized trial comparing 10-day DAC with ICT before allogeneic HSCT in patients ages 60 years old or older (NCT02172872). According to the current dogma that lowering leukemic burden is of tantamount importance before HSCT, especially with RIC, one can expect that the higher CR rate associated with ICT is to be preferred to HMAs in this context. However, there is, to date, no formal demonstration of this concept in AML. Furthermore, although ICT and HMAs differ by their CR rate in the global AML population, this may not be the case in all disease categories, especially in patients with poor-risk cytogenetics. Finally, not only the CR rate but also, the quality of these CRs are also likely to impact outcome after HSCT. Indeed, clonal remissions are frequent in this patient population after ICT[82] and may obviate prognosis after CR. Measurable residual disease as assessed by flow cytometry relying on Leukemia Aberrant Immunophenotype or leukemic stem cell markers[83,84] may also help compare these two strategies in a retrospective, nonrandomized fashion. Finally, one cannot neglect the different consequences that ICT vs AZA may have on the gut microbiome[85] and host immune system,[86] both of which may alter post-HSCT outcome.

Sequential combinations of chemotherapy and epigenetic therapy

ICT and HMAs are not mutually exclusive. To combine HMAs with standard induction chemotherapy seemed to be too toxic.[87] Using HMAs as postremission or maintenance therapy in patients in remission after ICT is attractive, because one may hypothesize a reduction in relapse incidence through the efficacy of epigenetic agents on residual MDS-like clonal hematopoiesis. This has been investigated,[88,89] and a British group has reported prolonged survival in older patients receiving AZA maintenance after achieving MRD-negative remission after ICT.[89] This contrasts with other reports not stratified on MRD, where DAC or low-dose AZA maintenance provided no obvious benefit compared with historical controls in AML patients in first CR.[90,91] A randomized trial is currently testing the role of oral AZA in this setting (NCT01757535).

Epigenetic therapy at relapse

Activity of HMA in R/R AML has mostly been reported retrospectively, with overall response rate in the 15% to 35% range, including 10% to 15% CRs, and median OS around 7 to 9 months, although prolonged survival, but not cure, was seen in patients reaching CR.[45,50,51,92] Prognostic factors in the R/R setting vary between reports, highlighting the differences in study populations. Some studies stressed the role of CR duration and BM blast percentage,[50,92] whereas others stressed the importance of cytogenetics and the presence of peripheral blasts.[51] Despite differences in study populations, the convergent median survival values seen in these series, which are comparable with other approaches of intermediate-intensity chemotherapy in R/R AML, nevertheless provide a coherent benchmark for the wealth of ongoing phase 2 trials in this setting, where single-agent HMA is often included as a reference arm.

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