Treatment of Newly Diagnosed AML in Unfit Patients

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Norbert Vey

10.1 Introduction

As demonstrated by large population-based studies (Menzin et al. 2002; Juliusson et al. 2009), the majority of older patients with acute myeloid leukemia (AML) are deemed ineligible for intensive chemotherapy (ICT; i.e., regimens based on the combination of anthracyclines and cytarabine), which is the standard of care for AML in children and young adults. In the Swedish registry (Juliusson et al. 2009), more than 90% of patients younger than 65 years received ICT as compared to 45% of those older than 65 years. Historically, unfit patients who were ineligible for intensive treatment approaches may have received only supportive care. Given that this population is projected to increase due to demographic changes and improved life expectancy, the improvement of their therapeutic options is of paramount importance. The recent development of low-intensity therapies over the past few years has thus provided an alternative to the typically binary choice between intensive treatment and no treatment at all.

The concepts of both low-intensity therapy and unfit patients have unclear definitions as they are often defined by default, that is, "low-intensity" automatically applies to any therapy that is not intensive induction/consolidation chemotherapy, while an "unfit" patient is any patient that cannot tolerate an intensive treatment. Patient outcomes result from the interactions of variables related to (1) the patient, (2) the disease, and (3) the treatment. From this perspective, the treatment of older unfit AML patients with low-intensity approaches is a losing battle fought with weak therapies (low-intensity having been synonymous with low-efficacy until recently) against resistant AML cells as reflected by the frequency of adverse cytogenetics and secondary AML (Vey 2013) in fragile patients with an increased risk of toxicity and treatment-related mortality. Fortunately, substantial progress has been made over the past decade with improvements in supportive care, identification of the most fragile patients, AML genetic-risk stratification, and new therapeutic approaches.

In this chapter, we will discuss the current definition of patient fitness and review treatment results for low-intensity approaches and their impact on the clinical management of AML. We will focus on low-dose cytarabine (LDAC) and and hypomethylating agents (HMA), which represent the current standard of care for unfit AML patients. We will also discuss the attempts made to improve these therapies with their combination to a variety of agents and the recent advent of more effective regimens based on the addition of venetoclax. Treatments based on therapies that target oncogenes, such as FLT3 or IDH1 and IDH2, are discussed in another chapter of this book.

N. Vey (✉)
Hematology Department, Institut Paoli-Calmettes, Aix-Marseille Université, CRCM, Marseille, France
e-mail: VEYN@ipc.unicancer.fr

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10.2 Who Is Unfit?

To date, there is no clear and univocal answer to this question, though consensus criteria have emerged that now form the basis of current eligibility criteria for clinical trials dedicated to unfit AML patients. Attempts to formalize criteria by which unfitness can be defined have been based on retrospective studies. The goal of these studies was to identify variables that predict a poor outcome following ICT such as low response rate, high early mortality (30- to 60-day mortality rate), or poor overall survival. In most of these studies, the following were independently associated with a poor patient outcome: age > 75 years, performance status (PS) > 2, hematopoietic cell transplantation comorbidity index (HCT-CI) > 3, high white blood cell counts (WBCs), and unfavorable cytogenetics (Etienne et al. 2007; Malfuson et al. 2008; Kantarjian et al. 2010). Sorror et al. recently proposed a scoring system built on the basis of a large retrospective study's results from 1100 AML patients aged 20–89 years (Sorror et al. 2017). Comorbidities, including those already incorporated into the HCT-CI (Sorror et al. 2005), were evaluated. The addition of parameters such as hypoalbuminemia and thrombocytopenia, a high level of lactate dehydrogenase, age, and European LeukemiaNet (ELN) risk categories further improved the model. The proposed AML-composite model (AML-CM) allowed for the identification of four risk groups with one-year overall survival of 84%, 65%, 52%, and 21%. Concerning patients aged 65–75 years, the two intermediate categories were associated with the same one-year overall survival and could be merged. The three subsequent risk categories were associated with one-year overall survival of 86%, 50% and 23%. As proposed by the authors, the first group would benefit from an intensive approach while the third clearly would not. With 50% one-year overall survival, there is some uncertainty as to whether the intermediate group would benefit from intensive or low-intensity therapy and may represent the appropriate target population for randomized trials.

Three important limitations of the proposed definition criteria for unfitness should be noted. First, with the exception of a single study (Sorror et al. 2017), the criteria are derived from analyses of intensively treated patient populations. Second, PS changes and certain comorbidities may be confounded with potentially reversible leukemia-related complications such as anemia, infection, and hyperleukocytosis. It is therefore advisable to reassess patients after correcting complications such as these in order to avoid an overestimation of a patient's unfitness. The third limitation is linked to insufficient awareness of the multiple dimensions of frailty in older patients. These include physical function, polypharmacy, cognition, social support, and nutritional status (Loh and Klepin 2018). A comprehensive geriatric evaluation of older AML patients revealed that more than 30% had significant cognitive impairment. The Short Physical Performance Battery (SPPB) was able to identify patients at high risk of early mortality among patients with a performance status of 0 to 1 (Klepin et al. 2013).

As reflected by several recommendations for AML management in older patients, age, performance status, comorbidities, and disease features, as well as patient wishes and physician appraisals, are major determinants in the decision-making process (Ferrara et al. 2013; Dohner et al. 2017). The results of the British Medical Research Council (MRC) AML-14 trial (Wheatley et al. 2009) have highlighted the importance of physician assessments. Initially, this trial planned to randomize patients to intensive or nonintensive treatment, but only eight were randomized out of 1485 patients included in the trial. When examining the variables associated with treatment modality decisions in centers where both treatment types were available, the physician emerged as a significant independent factor, after PS and age, in multivariate analysis. In the large study by Sorror et al., 20% of all patients received low-intensity treatment but this varied from 4 to 33% among the five participating centers (Sorror et al. 2017). This variability was not explained by differences in patient characteristics, further illustrating the subjectivity in

treatment choice even between highly specialized centers. Some may argue that an experienced physician's assessment may be as good as an imperfect scoring system; however, Bories et al. demonstrated that, besides their expertise, a physician's behavioral characteristics and in particular their individual attitudes toward risk and uncertainty have an impact on the decision-making process for older patients with AML (Bories et al. 2018). Thus, it is important to base treatment decisions on objective criteria and utilize stratification systems, such as the one proposed by Sorror et al. (Sorror et al. 2017), or simpler systems such as the one proposed by the Italian GIMEMA group, which used a consensus-based process to define unfitness according to the following criteria: age > 75 years, poor PS, and severe cardiac, pulmonary, renal, or other comorbidities (Ferrara et al. 2013).

10.3 Treatment with Low-Dose Cytarabine

10.3.1 Single-Agent LDAC

The efficacy of single-agent cytarabine has been known since the '60s (Lichtman 2013). Two randomized studies showed that overall survival was similar between older AML patients treated with single-agent low-dose cytarabine (LDAC) as compared to conventional induction chemotherapy (Lowenberg et al. 1989; Tilly et al. 1990). Yet in spite of its 50-year history, there is currently no established schedule and it remains unclear as to whether LDAC activity relates to cytotoxicity or to induction of differentiation. Following a large study conducted by the British Medical Research Council (MRC AML-14 trial), which compared LDAC to best supportive care (BSC) in older AML patients who were ineligible for ICT (Burnett et al. 2007), the use of a 20 mg twice daily for 10 days dose-schedule is currently widely used and serves as a control arm in the majority of recent trials. Their results indicated that LDAC produced a complete remission (CR) rate of 18% that translated into significantly prolonged overall survival as compared to BSC. Another important finding of this study was that the oldest patients derived the same benefit from LDAC as younger patients and that LDAC was ineffective in AML with adverse cytogenetics. Table 10.1 summarizes the results of seven clinical trials conducted on LDAC. A meta-analysis that included most of these trials revealed a pooled CR/CRi rate of 19% (95% CI [13%–27%]) and a pooled median overall survival of 5.4 (95% CI [4.4–6.7]) (Stone et al. 2019). The 60-day mortality rates, which reflect both efficacy and treatment toxicity, ranged from 18 to

Table 10.1 Patient characteristics and outcomes for those treated with LDAC in recent multicenter prospective trials

Study	No. of pts.	Median age	Adverse cytogenetics (%)	Median No. of cycles	CR (%)	60-day mortality	Median OS (months)
AML14 (Burnett et al. 2007)	103	74	17	2	18	29%	NR
AML AZA-001 (Dombret et al. 2015)	158	75	34	4	26	NR	6.4
DACO-016 (Kantarjian et al. 2012b)	215	73	36	2[a]	11.3	23%	5.0
Glasdegib-LDAC phase III trial (Cortes et al. 2018)	44	75	43	2	5.3	NR	4.3
Volasertib-LDAC phase II trial (Dohner et al. 2014)	42	76	39	2	13	18%	5.2
Sapacitabine vs. LDAC (Burnett et al. 2015)	73	75	17	3	28	23%	5.9
Lintuzumab-LDAC (Sekeres et al. 2013)	104	70	48	3	NR	NR	5.1

CR complete response, *LDAC* low-dose cytarabine, *NR* not reported, *OS* overall survival, *Pts* patients
[a]LDAC dose schedule was 20 mg/m^2 once daily for 10 days in this study and 20 mg twice daily in all others

29% (Burnett et al. 2007; Kantarjian et al. 2012b; Dohner et al. 2014; Burnett et al. 2015). Median ages were consistent across trials (median age ranged from 73 to 76 years), while the proportion of patients with adverse cytogenetics varied widely from 17 to 48% (Burnett et al. 2007; Kantarjian et al. 2012b; Sekeres et al. 2013; Dohner et al. 2014; Burnett et al. 2015; Dombret et al. 2015; Cortes et al. 2018). Factors predicting LDAC response have not been formally evaluated but some trends can be observed. An age of greater than 75 years was significantly associated with decreased overall survival in a meta-analysis (Stone et al. 2019). The detrimental effect of adverse cytogenetics was reported in a pooled analysis of all patients treated with lintuzumab-LDAC or LDAC alone with a median overall survival of 4.5 months in the group with adverse cytogenetics as compared to 8.7 months in the other patients ($P = 0.002$) (Sekeres et al. 2013). A similar trend was observed in two other studies (Burnett et al. 2007; Dohner et al. 2014). A poor PS was also associated with a trend toward worse outcomes (Burnett et al. 2007). There was no clear difference in patient outcome according to the LDAC dose-schedule. In the DACO-016 trial (Kantarjian et al. 2012b), LDAC was given once daily with 20 mg/m^2/day as opposed to the other trials presented in Table 10.1, which used the MRC AML-14 schedule. The response rate was lower (11.3%) in the DACO-016 trial but the overall survival was similar to that of the other trials.

10.3.2 LDAC-Based Combination Regimens

Several attempts have been made to improve LDAC results with the addition of new drugs. The MRC developed a "Pick a Winner" program devised to screen for new active therapies, mainly in combination with LDAC and compared to LDAC alone following random allocation (Hills and Burnett 2011). Based on previous experience, the program operated under the hypothesis that the CR rate would be a reliable surrogate for survival. Four new LDAC combinations have been tested using the anti-CD33 antibody–drug conjugate gemtuzumab ozogamicin (Burnett et al. 2013), arsenic trioxide (Burnett et al. 2011), the farnesyltransferase inhibitor tipifarnib (Burnett et al. 2012), or the quinolone-derived intercalating agent vosaroxin (Dennis et al. 2015). There was no indication of any improvement in patient outcomes as compared to the LDAC alone arm. However, the gemtuzumab ozogamicin combination achieved a significantly better CR/CRi rate, but this did not translate into a survival improvement (Burnett et al. 2013). Similarly, volasertib, a small molecule inhibitor of Polo-like kinase I that induces cell cycle arrest and apoptosis, in combination with LDAC as compared to LDAC alone in a randomized phase II trial demonstrated enhanced overall response rates (31% vs. 13.3%, respectively) and a prolonged median overall survival (8 months vs. 5.2 months, respectively), but these results were not confirmed in a large phase III randomized trial (Dohner et al., European Hematology Association meeting 2016, Abstract S501).

Venetoclax has been evaluated in combination with LDA (Wei et al. 2019). Based on initial encouraging results, the VIALE-C study, a multicenter, randomized, phase 3 trial comparing Venetoclax-LDAC to LDAC alone has been conducted in adult patients with previously untreated de novo or secondary AML ineligible for intensive chemotherapy (Wei et al. 2020). 143 and 68 patients were randomized to venetoclax plus LDAC and LDAC alone, respectively. The study failed to meet its primary endpoint of improved OS with the addition of venetoclax to LDAC (7.2 vs. 4.1 months; HR = 0.75 [95% CI: 0.52, 1.07]; $P = 0.11$); however, an unplanned analysis with an additional 6 months of follow up showed a significantly superior median OS of 8.4 months for the venetoclax arm (HR 0.70; 95% CI 0.50–0.98; $P = 0.04$). The CR/CRi rates were 48% and 13% for the venetoclax plus LDAC arm and LDAC-alone arm, respectively. The combination of venetoclax plus LDAC was primarily associ-

ated with grade 3 to 4 hematologic adverse events.

Altogether, these results have indicated that while CR may be a prerequisite for survival improvement with LDAC, CR alone is insufficient and a superior CR rate does not guarantee a survival benefit. Although not reaching its primary endpoint, the VIALE-C trial showed that the combination of venetoclax with LDAC showed clinically meaningful outcome improvement.

Glasdegib is an oral smoothened (SMO) inhibitor recently approved by the FDA and EMEA for the treatment of AML in unfit patients in combination with LDAC. SMO is involved in the Hedghog pathway that has been shown to contribute to the maintenance and expansion of leukemic stem cells (Irvine and Copland 2012). The BRIGHT-1003 trial(Cortes et al. 2018) was a randomized open-label controlled phase 2 study that compared glasdegib-LDAC to LDAC in previously untreated elderly patients with AML or higher-risk MDS. Glasdegib (100 mg/day) was given orally on a continuous basis and LDAC (20 mg) was given subcutaneously twice daily for 10 days every 28 days. About 88 patients were allocated to the glasdegib/LDAC arm and 44 to the LDAC. About 124 patients had AML and 16 MDS. Half of them were older than 75 years. Thirty-two percent were classified in the adverse group of the ELN 2010 classification in the glasdegib/LDAC arm versus 42% in the LDAC arm. CR/CRi rate was significantly higher in the glasdegib/LDAC arm (17% vs. 2.3%, $P < 0.05$) and overall survival was significantly longer (8.8 months with glasdegib/LDAC vs. 4.9 months with LDAC, $P = 0.0004$). The most frequently reported AEs with glasdegib/LDAC were pneumonia, fatigue, dyspnea, hyponatremia, and sepsis. Although positive, this study showed poor results in terms of response and overall survival that are in the range of what has previously been reported with LDAC or HMA as single agents. In the absence of direct comparison with the other low-intensity regimens, the place of glasdegib/LDAC in the current AML treatment algorithm thus remains to be established.

10.4 Hypomethylating Agents

Epigenetic deregulation plays an important role in the pathogenesis of AML. Recurrent somatic mutations in key genes involved in the epigenetic machinery (DNMT3A, TET2, IDH1, IDH2, and ASXL1) are frequently observed in AML and preleukemic clones (Papaemmanuil et al. 2016). Therapies targeting DNA methyltransferases (DNMTs) have been investigated in MDS and AML. The hypomethylating agents, decitabine and azacitidine, are pyrimidine analogs acting as DNMT inhibitors. They induce global hypomethylation of cytosine residues at cytosine–guanine dinucleotide–rich gene promoters and distal enhancers critical for gene expression regulation (Glass et al. 2017). Both azacitidine and decitabine have been approved in the EU (but not in the US, although widely used off-label) for the frontline treatment of AML in older patients ineligible for ICT.

10.4.1 Azacitidine

The AZA AML-001 study compared the outcome of 488 patients aged 65 years and above with newly diagnosed AML who were randomly assigned to receive either azacitidine (75 mg/m^2/day subcutaneous injections for 7 days per cycle) or conventional care regimens (CCR, including LDAC, ICT, or BSC) (Dombret et al. 2015). Although it did not meet the primary endpoint, the study reported an improved median overall survival of 10.4 months with azacitidine versus 6.5 months with CCR ($P = 0.1$) that reached statistical significance in a prespecified analysis censoring patients that received AML treatment after discontinuing the study drug (stratified log-rank $P = 0.0190$). Interestingly, the overall CR/CRi rates were relatively low and not different between the azacitidine arm (27.8%) and the CCR (25.1%) arm.

10.4.2 Decitabine

Similarly, the DACO-016 phase III trial compared the efficacy of decitabine with treatment choice (TC, supportive care, or LDAC) in older

patients with newly diagnosed AML and poor or intermediate-risk cytogenetics (Kantarjian et al. 2012b). About 485 patients were randomly assigned to receive decitabine 20 mg/m^2/day intravenously for 5 days every 4 weeks or TC. The results demonstrated a nonsignificant increase in median OS with decitabine (7.7 months) versus TC (5.0 months; $P = 0.108$). An unplanned analysis with more events indicated the same median OS but a statistically significant difference ($P = 0.037$). The CR/CRi with incomplete platelet recovery (CRp) rate was 17.8% with decitabine versus 7.8% with TC. Alternative dose-schedules of decitabine have been developed including a 10-day schedule, which may be more effective than the 5-day schedule (Blum et al. 2010).

10.4.3 Guadecitabine

Guadecitabine is a hypomethylating dinucleotide of decitabine linked to guanosine. Guadecitabine is resistant to degradation by cytidine deaminase and has a prolonged half-life as compared to decitabine. An encouraging CR/CRi rate of 54% was reported in a randomized phase II trial conducted in treatment-naïve older AML patients treated with guadecitabine as 60 or 90 mg/m^2/day for 5 days, (Kantarjian et al. 2017). However, the ASTRAL-1 study that compared guadecitabine to the standard of care (azacitidine, decitabine, or LDAC) in unfit AML patients demonstrated no significant difference in CR rates (19% vs. 17.4% in the guadecitabine vs. control arms, respectively) and overall survival (median of 7.1 vs. 8.4 months in the guadecitabine vs. control arms, respectively) (Fenaux et al. 2019).

10.4.4 Predictors of Response to HMAs

Older age (Kantarjian et al. 2012b), a poor performance status (Thepot et al. 2014; Pleyer et al. 2016), high WBC counts at diagnosis (Kantarjian et al. 2012b), and adverse cytogenetics (Bories et al. 2014; Pleyer et al. 2016) were associated with poorer response rates and/or survival. However, it is worth noting that the group with adverse cytogenetics had the greatest survival benefit from HMAs as compared to conventional care regimens in a subgroup analysis of the AZA AML-001 trial (Seymour et al. 2010). As expected, prior exposure to HMAs before AML transformation was associated with poor survival (median 7.8 months) in a retrospective study of 32 patients (Talati et al. 2020). The analysis of a large international retrospective series of older AML patients treated with azacitidine identified three covariates independently associated with overall survival: ECOG (0 vs. 1–2 vs. 3–4), WBC count before AZA onset ($\leq 10 \times 10^9$/L vs. $>10 \times 10^9$/L), and cytogenetics (normal vs. abnormal) (Ramos et al. 2015). The European ALMA (E-ALMA) scoring system was designed on the basis of these results. As shown in Table 10.2, the E-ALMA system adequately discriminates between three risk groups with different OS and may help with decision-making.

Several studies have suggested that gene mutations can impact prognosis; the TET2, DNMT3A, and NPM1 gene mutations were associated with higher response rates and survival after treatment with azacitidine (Itzykson et al. 2011; Metzeler et al. 2012; Craddock et al. 2017), and the TP53 gene mutation with improved response after treatment with a 10-day schedule of decitabine (Welch et al. 2016).

10.4.5 Real-World Data

As reflected by the opposing opinions of the US and European agencies, the interpretation of the

Table 10.2 Distribution of risk categories, response rates, and overall survival by the European ALMA score (Ramos et al. 2015)

Risk group	Score	*N* (%)	CR rate (%)	Median OS
Favorable	0	44 (13.4)	36.4	17.6 months
Intermediate	1–2	237 (72)	19.8	10.6 months
Poor	3–4	48 (14.6)	14.6	4.5 months

CR complete remission, *N* number of patients, *OS* overall survival

results of the two pivotal studies is still a matter of debate (Kantarjian et al. 2012b; Dombret et al. 2015). However, HMAs are considered as the standard of treatment for older unfit AML patients as revealed by various recent treatment recommendations (Dohner et al. 2017; Tallman et al. 2019). Several studies have addressed the issue of the impact of HMAs in the real world and their results are summarized in Table 10.3. The majority of these studies focused on AML patients treated with azacitidine and in general the results of the AZA AML-001 trial (Dombret et al. 2015) were reproduced both in terms of response (CR/CRi rate between 17 and 23% vs. 28% for real-world studies versus AZA AML-001, respectively) and in terms of median overall survival (between 10 and 14 months vs. 10 months for real-world studies vs. AZA AML-001, respectively) (Bories et al. 2014; Pleyer et al. 2016; Talati et al. 2020).

In a comparison of 214 patients treated with azacitidine within the AZA AML-001 trial with 95 patients selected according to AZA AML-001 inclusion criteria (i.e., WBC < 30 G/L, marrow blasts >30%) in the Austrian registry, no difference in overall survival was observed between the trial and real-world groups (9.9 and 10.8 months, respectively; $P = 0.616$) (Pleyer et al. 2017). Interestingly, this was also true when compared to patients from the Austrian registry who did not fulfill the AZA AML-001 trial eligibility criteria.

10.4.6 Insights into the Mechanisms of Resistance to HMAs

Recent studies have investigated the mechanisms of HMA resistance. Although global hypomethylation is generally observed following treatment with HMAs, the correlation between methylation levels and response has not been consistently documented (Voso et al. 2014). A study of patients treated with decitabine for chronic myelomonocytic leukemia (CMML) demonstrated that the methylation of specific DNA sites rather than global methylation was associated with response (Merlevede et al. 2016). Interestingly, clinical responses were achieved without either decreasing the mutant allele burden or preventing the

Table 10.3 Characteristics and outcomes of unfit patients treated with HMAs in multicenter prospective trials or in retrospective real-world studies for previously untreated AML

Study	No. of pts.	HMA/ Schedule	Median age	Median WBC	Adverse cytogenetics (%)	Median No. of cycles	CR/CRi (%)/Time to response	Median OS (months)
AML AZA-001 (Dombret et al. 2015)	241	AZA/EMEA	75	3.1	35	6	28%/NR	10.4
DACO-016 (Kantarjian et al. 2012b)	242	DAC/20X5	73	3.1	36	4	28%/4.3 months	7.7
French ATU (Thepot et al. 2014)	149	AZA/EMEA and alternate	74	3.2	40	5	33%/4.7 months	4.7
Toulouse (Bories et al. 2014)	95	AZA/EMEA and alternate	76	2.3	45	6	19%/4.5 months	11.3
Italian registry (Bocchia et al. 2019)	306	DAC	75	NR	30	5	23%/NR	10
Moffitt CC (Talati et al. 2020)	255	AZA and DAC	76	3.3	31	NR	23%/NR	14.4
Austrian registry (Pleyer et al. 2016)	139	AZA/EMEA	76	NR	31	3	17%/3 months	12.9

NR not reported, *EMEA* EMEA approved dose schedule, i.e., 75 mg/m^2/day × 7 days, *alternate* alternate schedules, i.e., 75 mg/m^2/day days 1–5 and 8–9 or 50 mg/m^2/day × 7

emergence of new genetic alterations. In myelodysplastic syndromes (MDS), treatment with azacitidine was able to modify the subclonal distribution but founder clones were not eliminated (Unnikrishnan et al. 2017). In AML, the number of leukemic stem cells (LSC) as measured by lymphoid multipotential progenitor populations (LMPP) persistence was lower in responders to azacitidine but persisted in the majority and increased prior to relapse (Craddock et al. 2017). Altogether, these data confirmed that HMA clinical activity relies on epigenetic mechanisms and show that HMAs are unable to induce a clonal eradication. The persistence of LCS may explain why HMAs alone are unable to produce long-term disease-free survival, making combinations of HMAs with LCS-targeting drugs an attractive approach.

10.5 The Lessons of HMA Therapy: A Paradigm Shift

One striking observation on HMA therapies was the dissociation between response and survival, challenging the basis upon which the classical International Working Group (IWG) response criteria for AML were established (Cheson et al. 2003). Indeed, after conventional ICT the achievement of CR is associated with survival improvements, which is also true for relapsed AML (Vey et al. 1999) and for the oldest patients (Vey et al. 2004). However, in the AZA AML-001 study, the survival benefit of azacitidine was retained even after excluding the responders from the analysis (Dombret et al. 2015). Approximately 30% of patients without bone marrow response improved their cytopenia. This indicates that normal hematopoiesis could be restored in the absence of significant bone marrow blast reduction, which may partially explain the survival benefit. In the DACO-016 study, the achievement of transfusion independence was associated with a significant increase in survival (median overall survival of 9.8 months and 6.4 months for patients with and without hematologic improvement (HI), respectively; $P = 0.02$). In a posthoc analysis of the AZA AML-001 trial, Schuh et al. revealed that among patients who achieved a stable disease, those with HI with azacitidine had improved survival (median overall survival increase of 7.9 months), which was not the case for patients treated in the CCR arm (Schuh et al. 2017b). In the Austrian registry study (Pleyer et al. 2014), bone marrow response was not an independent predictor of survival, whereas HI was, suggesting that the disease's natural history may be modified by HMAs even in the absence of blast reduction. This is consistent with the epigenetic mechanisms and induction of differentiation. Comparable treatment effects have recently been observed with new therapies such as the IDH1 or 2 inhibitors ivosidenib and enasidenib, which also target epigenetic mechanisms and were shown to induce differentiation (Stein et al. 2020). Though HI is commonly used as a response criterion in MDS (Cheson et al. 2006) but not in AML (Dohner et al. 2017), it appears to be relevant for evaluating the effects of low-intensity therapies on AML and may be integrated into future AML response criteria (Bloomfield et al. 2018). This observation also has practical implications as it supports the recommendation to continue HMA therapy even in the absence of a response, so long as patients can tolerate the treatment and the disease does not progress (Estey 2013; Schuh et al. 2017a). In addition, registry data indicate that continuous treatment is more important than azacitidine dosage or dosing schedule regarding OS benefits, which is consistent with the transience of demethylation observed in HMA treatment (Thepot et al. 2014; Pleyer et al. 2014; Ramos et al. 2015).

10.6 HMA-Based Combination Regimens

Although the use of HMAs has led to significant improvements in the outcome of older unfit AML patients, results remain unsatisfactory with an overall median survival that does not exceed 1 year (see Table 10.3). Consequently, when this information is combined with the favorable tolerance profile of HMAs, they are regarded as attractive drugs for the design of novel combina-

tion regimens. Based on preclinical evidence demonstrating that the dual inhibition of epigenetic pathways via HMAs and histone deacetylase inhibitors (HDAC) leads to synergistic in vitro activity (Cameron et al. 1999), the combination of HMAs with HDAC has been extensively investigated. Regimens combining azacitidine or decitabine with a variety of HDAC, such as valproic acid, vorinostat, and entinostat, were studied in MDS and AML with disappointing clinical effects. This was possibly due to HDAC toxicity leading to early treatment interruption, not only of the HDAC but also of the HMAs, which may have counteracted the potential beneficial effects (Garcia-Manero et al. 2008; Griffiths and Gore 2013). Recently, encouraging results have been reported in a phase II study of pracinostat and azacitidine with a CR/CRi rate of 44% and a median overall survival of 19 months that need to be confirmed (Garcia-Manero et al. 2019). The antitumor immune response was positively affected by HMAs upregulating the expression of tumor antigens, HLA class-1, or co-stimulatory molecules, but this can be offset by the concomitant upregulation of inhibitory immune checkpoint molecules, which makes the combination of HMAs with immune checkpoints inhibitors appealing (Daver et al. 2018). Encouraging preliminary clinical results have been reported (Daver et al. 2017) but were not confirmed by the results of a randomized phase II study comparing durvalumab and azacitidine to azacitidine alone in previously untreated AML patients ineligible for ICT (Zeidan et al. 2019a). In many other instances, combination regimens have been developed empirically in the absence of biological rationale and were listed in Schuh's review article (Schuh et al. 2017a). Most of these attempts failed to improve patient overall survival as compared to HMA monotherapy, in spite of a substantial increase in the response rate. This underlines the importance of safety and tolerance issues in older fragile patient populations as illustrated by vadastuximab talirine (SGN-CD33A), an antibody–drug conjugate directed toward CD33 (Kung Sutherland et al. 2013). A phase I trial found that the combination of SGN-33A with AZA yielded responses in 70% of patients with the majority of them achieving MRD negativity (Fathi et al. 2018), but the phase III CASCADE trial comparing vadastuximab and HMAs to HMAs alone was put on hold due to excessive toxicity. In a study combining alternating courses of LDAC-cladribine and decitabine in 118 AML patients ineligible for ICT, Kadia et al. reported a CR/CRi rate of 68% and a median overall survival of 13.8 months, which compared favorably to decitabine alone (Kadia et al. 2018). It should be noted, however, that study patients had a median age of 69 years, a median ECOG performance status of 1, and 25% of them could receive transplantations. These characteristics correspond to those of older patients who are eligible for ICT (Pigneux et al. 2007; Lowenberg et al. 2009) rather than those of unfit patients (Kantarjian et al. 2012b; Dombret et al. 2015). This suggests that "intensified low-intensity" regimens may provide improved patient outcomes as compared to HMAs, but that not every unfit patient would be able to tolerate an increase in treatment intensity (Vey 2018).

Venetoclax in combination with azacitidine was evaluated versus azacitidine alone in the multicenter, randomized, phase 3 VIALE-A study (DiNardo et al. 2020). Eligible patients had newly diagnosed AML and were either aged ≥75 years or aged ≥18 years and considered ineligible for standard induction therapy based on the presence of prespecified comorbidities. The study included 286 patients in the venetoclax (VEN) plus azacitidine arm and 145 in the azacitidine plus placebo (PBO) arm. The addition of venetoclax to azacitidine was associated with improved OS (14.7 months in AZA + VEN vs. 9.6 mos in AZA + PBO (HR: 0.66, 95% CI: 0.52–0.85, $P < 0.001$)). CR + CRi rate was 66% and 28% in AZA + VEN and AZA + PBO respectively, $P < 0.001$). Venetoclax plus azacitidine was primarily associated with grade 3 and 4 hematologic adverse events and manageable gastrointestinal toxicity. The combination of venetoclax and HMA has been approved by the FDA in 2019. The confirmation of the efficacy of this regimen by the phase 3 VIALE-A trial makes it a new standard for the frontline therapy of elderly patients with AML unfit for intensive chemotherapy (Richard-Carpentier and DiNardo 2019).

10.7 LDAC Versus HMAs, Azacitidine Versus Decitabine: Did We Pick a Winner?

So far in randomized studies, HMAs have not demonstrated significantly superior survival to LDAC (Kantarjian et al. 2012b; Dombret et al. 2015). However, converging evidence suggests HMA superiority. As discussed above, overall results with LDAC are disappointing, with a median overall survival of less than 6 months in most studies. In addition, achieving CR with LDAC is generally restricted to patients with favorable or intermediate-risk cytogenetics, and survival benefits are mainly restricted to patients who achieve CR (Burnett et al. 2007). HMAs have also demonstrated several potential advantages over LDAC. First, HMAs produce higher HI rates as revealed by the AZA AML-001 study with a red blood cell (RBC) transfusion independence rate of 70% as compared to 17% in the control arm ($P = 0.03$) (Dombret et al. 2015) and this may translate into a survival benefit (Pleyer et al. 2014). Second, HMAs are effective in poor-risk genetic categories, such as inv(3) or TP53 mutations (Wanquet et al. 2015; Welch et al. 2016), with a statistically significant survival benefit in combination with azacitidine versus LDAC in the group with adverse cytogenetics (Döhner et al. 2014). Third, some real-world data provided additional evidence for the superiority of HMAs as compared to LDAC (Talati et al. 2020).

The comparison of azacitidine with ICT has not been directly addressed in comparative studies for the AZA AML-001 study. However, only 87 patients were randomized between azacitidine and ICT. The results showed a higher CR/CRi rate in the ICT arm (47% vs. 28% in the azacitidine arm) but a similar median overall survival (13.3 vs. 12.2 in the azacitidine arm, $P = 0.5$), yet given the small number of patients, no definitive conclusion could be drawn. Two single-institution retrospective studies that used propensity score-based analysis reported conflicting results with better overall survival for ICT versus azacitidine in one study (Bories et al. 2014) and the opposite in the other (Talati et al. 2020), where the proportions of patients treated with ICT were comparable (34% and 36.7%). Collectively, these results indicate that ICT yields higher CR rates as compared with azacitidine, but there is no clear evidence that this translates into better overall survival.

No prospective trial comparing azacitidine with decitabine has been reported as of yet. The available data are derived from indirect comparisons and retrospective studies in MDS and AML, suggesting that azacitidine is at least as effective as decitabine and may have a greater impact on overall survival (Kumar et al. 2010; Kantarjian et al. 2012b; Xie et al. 2015; Dombret et al. 2015). A recent large phase 3 trial compared guadecitabine to a control arm in which patients may receive azacitidine or decitabine based on physician choice. Respectively 171 and 167 patients were allocated to azacitidine or decitabine and they characteristics were well balanced. The composite CR rate (CR + CRi + CRp) was 22.2% vs. 25.1% and the median OS 8.7 vs. 8.2 (HR: 0.97; 95% CI: 0.77–1.23; Log-rank P value: 0.81).

10.8 Other Low-Intensity Therapies

In the pre-HMA era, since no established therapy was available, it was possible to include unfit patients with previously untreated AML in early phase trials, which had the advantage of allowing the evaluation of new drugs in treatment-naïve patients instead of the usual heavily pretreated refractory/relapsed patient populations. Many new agents have been tested in this setting and scarce responses have been achieved with most of them (Stahl et al. 2017), though few have been tested in phase III trials. The farnesyltransferase inhibitor tipifarnib was not associated with improved patient outcomes as compared to BSC in a randomized study (Harousseau et al. 2009). More recently, the orally available nucleoside analog sapacitabine has been investigated in unfit AML patients based on initial reports showing a favorable tolerance profile and significant activ-

ity in this setting (Kantarjian et al. 2012a). In a phase III trial of the British MRC comparing single-agent sapacitabine and LDAC (Burnett et al. 2015), the CR rate with sapacitabine was 16% while the median overall survival was 4.7 months, and these were not superior to LDAC.

10.9 Conclusion

Low-intensity therapies represent a significant advance in the clinical management of older patients with AML. Over the past decade, a growing proportion of older patients were offered therapy as shown by population-based studies and registries (Medeiros et al. 2015; Nagel et al. 2017; Talati et al. 2020). In a study of Surveillance, Epidemiology, and End Results(SEER)-Medicare data from 14,089 older patients with AML residing in the US, the proportion of patients who did not receive active treatment decreased over time from 59.7% among patients diagnosed in 2001 to 42.8% among those diagnosed in 2013 (Zeidan et al. 2019b).

Azacitidine and decitabine are effective new forms of low-intensity therapy and may be superior to LDAC. In large cohorts from specialized centers, HMAs are used in approximately one-third of patients older than 65 years (Bories et al. 2014; Talati et al. 2020), while less than 10% of patients received LDAC, highlighting the growing importance of HMAs in the current AML therapeutic armory. Existing data from clinical trials or retrospective studies indicate a survival benefit as compared to LDAC, particularly in patients with unfavorable cytogenetics who represent 35–40% of patients in this age group. Whether HMAs are superior or equivalent to ICT has not been established. With the currently dynamic AML therapeutic landscape, it is unlikely and probably undesirable to perform such studies. The new and more effective venetoclax-based low-intensity regimens that are currently being developed will challenge conventional ICT and their validation is now a priority.

HMAs have also revealed that epigenetic therapies do not have the same clinical effects as conventional chemotherapy. Indeed, the dissociation between response and survival, the transience of demethylation, and the achievement of hematologic improvements in the absence of blast reduction imply that treatment should be continued until progression, even in the absence of bone marrow response. This also demonstrates that achieving CR should not be a primary goal of any clinical trials evaluating these therapies and that hematologic improvements may represent a meaningful clinical endpoint as it does in MDS.

The development of novel active low-intensity therapies for older AML patients has emphasized the need for objective and reproducible criteria to define "unfitness." Several simple stratification systems have been developed as well as more sophisticated geriatric tools, and their implementation in clinical practice should improve physicians' decisions.

With the recently reported results of venetoclax-HMA combination (DiNardo et al. 2020), a new standard has emerged that will probably have a significant impact on the outcome of elderly patients with AML. However, even if improved, the survival of these patients remains short and further improvements are warranted. This will rely on the ongoing development of several novel agents as described in another chapter of this book that could be added to the venetoclax-HMA backbone or be incorporated into sequential strategies. This underlines the importance of including elderly patients in clinical trials.

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