

# Low-intensity regimens versus standard-intensity induction strategies in acute myeloid leukemia

Norbert Vey 

Ther Adv Hematol

2020, Vol. 11: 1–11

DOI: 10.1177/  
2040620720913010

© The Author(s), 2020.  
Article reuse guidelines:  
sagepub.com/journals-  
permissions

**Abstract:** Treatment options for elderly patients with acute myeloid leukemia (AML) remain limited. In this age group, AML is frequently associated with poor-risk features, while patients' present comorbidities and reduced functional reserves. As such, intensive chemotherapy (ICT) is frequently too toxic or ineffective in elderly patients and is restricted to a select minority, though it is standard therapy for the youngest and fittest patients or for those belonging to either the favorable or intermediate-risk groups. The use of hypomethylating agents represent an effective alternative for patients who are unfit for ICT, yet the results remain unsatisfactory. In recent years, prognostic scores were developed that include geriatric assessment tools and improved risk-stratification. In addition, several effective new drugs have emerged. The combination of these drugs with hypomethylating agents or low-dose cytarabine has produced encouraging preliminary results that may change standard practices and offer an alternative to the dilemma of ICT *versus* low-intensity therapies.

**Keywords:** acute myeloid leukemia; elderly; hypomethylating agents; low-dose cytarabine; intensive chemotherapy

Received: 23 July 2019; revised manuscript accepted: 12 February 2020.

## Introduction

The effective treatment of acute myeloid leukemia (AML) remains a challenge in older patients. This age group represents the majority of AML patients as the median age at diagnosis is 65 years and disease incidence increases steeply with age, reaching 70 new cases per 100,000 after the age of 75 years.<sup>1,2</sup> Many factors associated with chemotherapy resistance are linked to AML in elderly patients including: adverse karyotypes, immature phenotype, and expression of efflux pumps.<sup>3</sup> In addition, elderly patients often present comorbidities and reduced functional reserves, which are associated with increased treatment-related mortality and represent contraindications to the use of intensive chemotherapy (ICT). Consequently, population-based studies have shown that 50% to 70% of elderly patients are not offered ICT,<sup>4–6</sup> and those few that are eligible have a generally better outcome<sup>7–9</sup> when compared with those deemed unfit for ICT with a median overall survival (OS) of 12 months *versus* 3 to 10 months, respectively.<sup>10–12</sup>

However, there have been several advances during the past decade that attempt to address this issue, such as the optimization of ICT regimens<sup>8</sup> and the use of nonmyeloablative conditioning regimens for allogeneic stem cell transplantation (SCT),<sup>13</sup> while the development of therapies utilizing hypomethylating agents (HMAs) has provided an effective alternative to ICT.<sup>14</sup> In addition, the difficulty in choosing between intensive *versus* nonintensive therapy has been eased *via* both improved risk stratification<sup>15,16</sup> and the development of geriatric assessment tools.<sup>17</sup> In fact, the year 2017 was a landmark for innovative AML therapies.<sup>18</sup> Since then, no fewer than eight different drugs have obtained United States (US) Food and Drug Administration (FDA) approval for AML treatment, thereby creating a highly dynamic and rapidly evolving therapeutic landscape. Low-intensity therapies have been particularly impacted by this since many new drugs can be safely combined with HMAs, allowing for the development of effective new combination regimens that may challenge the use of ICT in the elderly AML population.

Correspondence to:  
**Norbert Vey**  
Institut Paoli-Calmettes,  
232 Boulevard de Sainte  
Marguerite, Marseille,  
13009, France

Univ-med Aix Marseille,  
IPC Department of  
Hematology and CRCM,  
Marseille, France  
veyn@ipc.unicancer.fr



Therefore, in order to better understand the factors necessary for deciding between ICT and low-intensity therapies, in this paper we review the current relevant data and discuss how new therapies may offer alternatives to the low- *versus* high-intensity dilemma.

### Intensive chemotherapy

Standard ICT is a combination of anthracyclines (daunorubicin or idarubicin) and cytarabine. Recent multicenter cooperative group studies have reported complete response (CR) rates ranging from 60% to 70% and a median OS of 12 months in patients older than 60 years.<sup>7–9,19</sup> The HOVON group demonstrated that daunorubicin doses of 90 mg/m<sup>2</sup> yielded improved CR rates when compared with 45 mg/m<sup>2</sup>. A survival benefit was also established, but the effect was restricted to patients aged 60–65 years.<sup>8</sup> Several attempts have been made to improve the results of conventional two-drug ICT regimens *via* the addition of a third drug. Gemtuzumab ozogamicin, an antibody–drug conjugate, when combined with daunorubicin and cytarabine was associated with a significantly higher 2-year event-free survival (EFS) than the daunorubicin–cytarabine control group (40.8% *versus* 17.1%, respectively) in patients aged 55–70 years.<sup>9</sup> Another study found that the addition of lomustine, an oral alkylating agent, was associated with an improved response rate and prolonged OS compared with the control group in patients older than 60 years.<sup>7</sup> Finally, the addition of cladribine was demonstrated to benefit a subset of elderly patients with AML aged 60–65 years in a prospective randomized phase II trial of a Polish cooperative group.<sup>20</sup>

It is worth noting that in several studies the improvements achieved by the intensification of a standard daunorubicin–cytarabine regimen did not benefit the oldest patients (i.e. those older than 65 years), which highlights the need for new strategies for these patients.<sup>8,20</sup>

CPX-351 is a liposomal formulation of daunorubicin and anthracycline encapsulated at a fixed molar ratio; recently approved by the US FDA and European Medicines Agency for first-line treatment of secondary AML. In a phase III randomized trial including 309 patients aged 60–75 years with newly diagnosed secondary AML [defined as therapy-related AML, AML with a history of myelodysplastic syndrome (MDS) or

chronic myelomonocytic leukemia (CMML), or *de novo* AML with MDS-related cytogenetic abnormalities], CPX-351 treatment compared with the control group who received conventional ICT was associated with a significantly higher CR rate [CR/CR with incomplete hematological recovery (CRi): 47.7% *versus* 33.3%, respectively;  $p=0.016$ ], improved survival (12-month OS: 41.5% *versus* 27.6%, respectively), and reduced early mortality (60-day mortality: 13.7% *versus* 21.2%, respectively), although the survival benefit was not reported in the group with unfavorable cytogenetics. The additional finding that more patients in the CPX-351 group received an allogeneic SCT than those in the control group (34% *versus* 25%, respectively) further reflects the improved efficacy and tolerance, and suggests that CPX-351 may fill the gap between low-intensity and intensive regimens, at least for a subset of patients.<sup>21</sup> Another interesting study illustrated the difficulty in balancing efficacy and toxicity in this challenging subset of patients. Walter and colleagues evaluated the use of reduced doses of CPX-351 (32 or 64 units/m<sup>2</sup>) in patients with comorbidities and found that a reduction of treatment-related mortality could not be achieved while maintaining the CR rate.<sup>22</sup>

For patients who achieve CR, the administration of additional chemotherapy is generally deemed necessary, although no standard postremission therapy has been established thus far. The ALFA-9803 trial compared the administration of one course of intensive consolidation (daunorubicin 45 mg/m<sup>2</sup>/day or idarubicin 9 mg/m<sup>2</sup> for 4 days in combination with cytarabine 200 mg/m<sup>2</sup> IV for 7 days) with repeated cycles of less-intensive consolidation courses (either 45 mg/m<sup>2</sup> daunorubicin or 9 mg/m<sup>2</sup> idarubicin for 1 day in combination with 60 mg/m<sup>2</sup>/12 h cytarabine for 5 days), in elderly patients (age > 50 years) in first CR. Its results showed improved relapse-free survival in the nonintensive consolidation arm.<sup>23</sup> In line with these data, the Cancer and Leukemia Group B (CALGB) 8923 study found that the administration of four courses of low-dose cytarabine (LDAC) was associated with similar survival results as two courses of intermediate-dose cytarabine and mitoxantrone.<sup>24</sup>

Maintenance therapy represents another form of postremission therapy. In a study from the HOVON group, patients randomized to receive 1-year of maintenance with azacitidine had a

significantly better 12-month disease-free survival compared with the control group (64% *versus* 42%, respectively) although OS was not improved, most likely due to the use of different salvage therapies.<sup>25</sup> This study was the first to demonstrate an improvement in patient outcomes with the use of maintenance in nonpromyelocytic AML and paved the way for future investigations that will take advantage of the new orally available targeted drugs currently in development.

Allogeneic SCT is the most potent therapy in preventing AML relapses. With the recent development of nonmyeloablative conditioning regimens, more elderly patients have become eligible for allogeneic SCT. Data from the Center for International Blood and Marrow Transplant Research indicate that the number and proportion of elderly patients receiving a transplant in the US has increased markedly over the past decade and was associated with significant survival improvements after the transplant.<sup>13</sup> Eligibility for ICT and transplantation follows the same criteria and the two strategies must be considered as complementary, especially as ICT, which is associated with high remission rates, currently remains the most effective strategy to 'bridge' the patients to the transplant.

Recently emerging targeted therapies can also be combined with standard ICT to potentially produce more active regimens. Midostaurin is a multikinase FLT3 inhibitor that is used to treat FLT3-mutated AML and was recently approved by the US FDA and European Medicines Agency based on the results of a large randomized trial conducted in younger patients.<sup>26</sup> In a noncomparative prospective study of midostaurin in combination with ICT, Schlenk and colleagues reported comparable effectiveness between older and younger patients, in which the CR/CRi rate in older patients was 77.9% and the 2-year EFS was 33%. Using a propensity score-based analysis, elderly patients treated with midostaurin and ICT had a significant improvement in both EFS and OS compared with historical controls. A significantly higher rate of cardiac toxicity and a nonsignificant trend toward higher pulmonary toxicity were observed in older patients, though there was no excess early mortality. However, this indicates that the addition of midostaurin might increase toxicity and should be used with caution in the oldest patients.<sup>27</sup> Other targeted agents such as the IDH1 and IDH2 mutant inhibitors ivosidenib and enasidenib have shown clinical activity as single

agents in patients with refractory/relapsed IDH-1 and IDH-2 mutated AML.<sup>28,29</sup> Similarly to FLT3-inhibitors, their evaluation in combination with ICT is currently ongoing.<sup>30</sup>

#### *Low-intensity regimens for AML*

Standard low-intensity regimens utilize LDAC or HMAs. LDAC corresponds to various dose schedules with doses inferior to 50 mg/day given as subcutaneous injections. No standard schedule has yet been established although most recent trials use doses of 20 mg twice daily for 10 days in 28-day cycles. A study from the Medical Research Council found that LDAC was more effective than hydroxycarbamide and best supportive care with a higher CR rate and a prolonged OS.<sup>10</sup> In that study, patient outcome was poor with a CR rate of 18%, a median OS of only 10 weeks, and no response in patients with poor-risk cytogenetics.

Modern low-intensity therapies have emerged with the development of HMAs.<sup>31</sup> Although associated with substantial hematologic toxicity, the limited nonhematologic toxicity of these drugs made them appropriate for the treatment of frail patients. In the AML001 study, 488 patients aged 65 years and above with newly diagnosed AML were randomly assigned to receive azacitidine or conventional care regimens (CCRs; including LDAC, intensive chemotherapy, or best supportive care). Although the primary endpoint was not met, the study reported an improved median OS of 10.4 months with azacitidine *versus* 6.5 months for CCR ( $p=0.1$ ), which reached statistical significance in a prespecified analysis censoring patient who received AML treatment after discontinuing the study drug (stratified log-rank  $p=0.0190$ ). Overall response (CR/CRi) rates were comparable between the azacitidine (27.8%) and CCR (25.1%) arms.<sup>11</sup>

A phase III trial compared the efficacy of decitabine with treatment choice (TC) in older patients with newly diagnosed AML and poor- or intermediate-risk cytogenetics. A total of 485 patients were randomly assigned to receive decitabine 20 mg/m<sup>2</sup>/day intravenously for 5 days every 4 weeks or TC (supportive care or LDAC). The results demonstrated a nonsignificant increase in median OS with decitabine (7.7 months) *versus* TC (5.0 months;  $p=0.108$ ), but an unplanned analysis with additional events indicated the same

median OS but with a statistically significant difference ( $p=0.037$ ). The CR/CR with incomplete platelet recovery rate was 17.8% with decitabine *versus* 7.8% with TC.<sup>12</sup> Alternative dose schedules of decitabine have been developed including a 10-day schedule.<sup>32</sup>

Based on these results, azacitidine and decitabine were registered for the treatment of AML in elderly patients not eligible for ICT in the European Union but not in the US (although there is widespread off-label use). Advanced age,<sup>12</sup> a poor performance status,<sup>33,34</sup> high white blood cell counts at diagnosis,<sup>12</sup> and adverse cytogenetics were all associated with poor response rates or survival.<sup>33,35</sup> However, it is worth noting that the group with adverse cytogenetics had the greatest survival benefit with HMAs compared with CCR in a subgroup analysis of the AML-001 trial.<sup>36</sup> This effect is particularly seen in those with chromosome 3q abnormalities, which are associated with resistance to conventional chemotherapy and for which azacitidine has been shown to be effective.<sup>37</sup> Several studies have suggested that gene mutations can impact prognosis, such as TET2, which was associated with increased survival after treatment with azacitidine,<sup>38</sup> DNMT3A with improved response after treatment with decitabine,<sup>39</sup> and TP53 with improved response after treatment with a 10-day schedule of decitabine.<sup>40</sup>

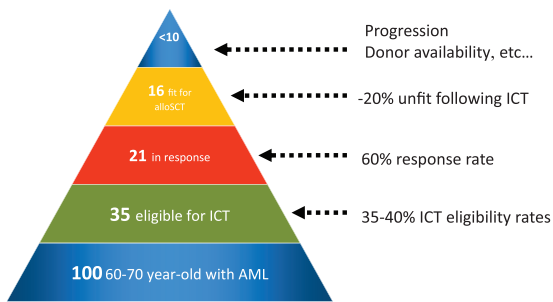
Guadecitabine is a hypomethylating dinucleotide of decitabine linked to guanosine. Guadecitabine is resistant to degradation by cytidine deaminase and has a prolonged half-life compared with decitabine.<sup>41</sup> In a randomized phase II trial comparing three dose regimens of guadecitabine (60 mg/m<sup>2</sup>/day for 5 or 10 days and 90 mg/m<sup>2</sup>/d for 5 days), the best response rates were achieved with the regimen of 60 mg over 10 days (composite CR rate of 30.2%). Adverse events were mainly hematologic, with a higher incidence in the 10-day regimen.<sup>42</sup> Another randomized phase II trial,<sup>43</sup> was conducted in previously untreated elderly patients with AML, in which the CR/CRi rate was 54%. The ASTRAL-1 study (ClinicalTrials.gov identifier: NCT02348489) compared guadecitabine (60 mg/m<sup>2</sup> 5-day schedule) with standard care (azacitidine, decitabine, or LDAC) in adults with previously untreated AML who were ineligible for intensive induction chemotherapy. The study failed to demonstrate a superiority of guadecitabine in terms of CR (19% in the guadecitabine arm) and survival (median

of 7 months in the guadecitabine arm). (Fenaux and colleagues, oral abstract no. S879. 15 June 2019, European Hematology Association 24th Annual Meeting, Amsterdam, The Netherlands).

Altogether, these results indicate that HMAs represent suitable alternatives to ICT for elderly patients who cannot tolerate chemotherapy or for patients with unfavorable-risk cytogenetics for whom chemotherapy is ineffective. However, these results need to be improved, which could be achieved by the addition of new compounds to an HMA ‘backbone’.

#### *Intensive chemotherapy versus low-intensity therapies: how to choose?*

In the absence of a formal prospective comparison of ICT and HMAs in elderly patients with AML, there is no definitive answer to this question. In the AML001 study, the number of patients included in the azacitidine *versus* ICT randomization was too small to draw any conclusion.<sup>11</sup> A retrospective study from a single French institution using propensity scores found no difference in the outcomes of elderly patients treated with ICT compared with those treated with HMAs.<sup>35</sup> In real-life studies reporting elderly AML treatment results, two different patient profiles can be distinguished. In the first, patients with intensive treatments are usually younger, have fewer comorbidities, higher white blood cell counts at diagnosis, and favorable or intermediate-risk cytogenetics. Whereas in the second, patients treated with HMAs are usually older, have secondary AML, numerous comorbidities, a high Eastern Cooperative Oncology Group (ECOG) performance status, and unfavorable-risk cytogenetics.<sup>14</sup> Several attempts have been made to model these profiles and scoring systems that integrate the different prognostic markers have been developed.<sup>44–46</sup> Sorror and colleagues recently published the results of a retrospective cohort study conducted in 1100 patients who were 20–89 years of age and treated for AML. Comorbidities, including those already incorporated into the Hematopoietic Cell Transplantation-Comorbidity Index, were evaluated.<sup>47</sup> The addition of parameters such as hypoalbuminemia, thrombocytopenia, high lactate dehydrogenase level, age, and European LeukemiaNet (ELN) risk categories further improved the prognostic prediction of the model. Interestingly, age was found to retain prognostic significance even when accounting for the effects of covariates.<sup>16</sup>



**Figure 1.** Schematic representation of the distribution of patients across the steps of an intensive treatment approach, based on 100 elderly patients with newly diagnosed AML. AML, acute myeloid leukemia; ICT, intensive chemotherapy.

One important limitation of the proposed models is their omission of important dimensions of vulnerability in older patients, such as physical function, polypharmacy, cognition, social support, and nutritional status, which are included in the comprehensive geriatric evaluation that can be used in patients with AML as for solid tumors. Using this tool, researchers discovered that more than 30% of patients with AML older than 70 years had significant cognitive impairment.<sup>48</sup> The Short Physical Performance Battery was used to identify a subgroup of patients with increased risk of early mortality among patients with an ECOG performance status of 0–1.<sup>49</sup> However, geriatric assessment tools are not widely used and guidelines for the determination of fitness still recommend assessments based on classical parameters such as age, performance status, and comorbidities.<sup>15</sup>

Another limitation of the current definition of ‘unfitness’ is that it mixes patient-related factors (associated with treatment toxicity) with disease-related factors (associated with leukemia resistance). In the previous era of chemotherapy when toxicity and efficacy were closely linked, this composite definition of fitness made sense, but treatment options are changing and patient fitness should be distinguished from treatment appropriateness.<sup>48</sup>

In conclusion, ICT benefits a subset of elderly patients with AML characterized by a younger age (i.e. less than 75), good performance status, few comorbidities, and with an AML belonging to either the favorable or intermediate-risk ELN 2017 categories.<sup>50</sup> For these patients, the higher rates of and shorter time to response provided by ICT

make it the optimal option for a bridge to transplantation. However, in real-life, there is a high dropout rate at every step of AML treatment starting at the initial treatment decision. As highlighted in Figure 1, less than 10% of elderly patients with AML will ultimately undergo transplantation.

#### *How to escape the dilemma? The new generation of low-intensity regimens*

Several attempts have been made to improve the antileukemic activity of low-intensity regimens with the addition of a new agent to HMA or LDAC backbones. An overview of the novel drugs that have been recently tested can be found in a review by Stahl and colleagues.<sup>51</sup> The rationale for combining HMAs with a novel drug was based on preclinical reports that indicated synergy with HMAs for certain drugs, such as histone deacetylase inhibitors<sup>52,53</sup> or immune checkpoint inhibitors,<sup>54</sup> but in most instances the second drug was chosen on an empirical basis. A summary of the different studies conducted over the last 10 years is included in Table 1. Although many phase I–II combination trials provided encouraging results, these have not been confirmed in large randomized trials due to either a lack of efficacy or excessive toxicity in the new regimens. This was the case with SGN-CD33A, a monoclonal antibody directed towards CD33 conjugated with a DNA-crosslinking pyrrolobenzodiazepine dimer.<sup>55</sup> A phase I trial found that the combination of CD33A with azacitidine yielded responses in 70% of patients with the majority of them achieving Minimal residual Disease (MRD) negativity,<sup>56</sup> but the phase III CASCADE trial comparing vadastuximab and HMAs with HMAs alone was put on hold due to excessive toxicity. Similarly, volasertib, a small molecule inhibitor of Polo-like kinase I that induces cell cycle arrest and apoptosis, in combination with LDAC demonstrated enhanced overall response rates (31% *versus* 13.3%, respectively), prolonged EFS (5.6 months *versus* 2.3 months, respectively), and OS (8 months *versus* 5.2 months, respectively) compared with LDAC alone.<sup>57</sup> These results were not confirmed in a phase III randomized trial when the volasertib/LDAC arm was associated with a negative trend in OS and a significantly higher incidence of adverse events compared with LDAC alone (Dohner and colleagues<sup>50</sup>, European Haematology Association meeting, 2016). These two examples reveal that the toxicity of these regimens had been underestimated in the early-phase

**Table 1.** Summary of HMA/LDAC-based combination regimen for unfit patients with AML.

Backbone	New drug	No. of patients	Median age	Randomization	CR/CRi	OS	Reference
AZA	SGN003	53	75	No	70%	11.3 m	Fathi and colleagues <sup>56</sup>
AZA	Nivolumab	10	75	No	56%	NA	Daver and colleagues <sup>54</sup>
AZA	Pevonedistat	64	75	No	50%	7 m	Sword and colleagues <sup>58</sup>
AZA	Pracinostat	50	75	No	46%	19.1 m	Garcia-Mannero and colleagues <sup>59</sup>
AZA or DAC	Venetoclax	145	74	No	67%	11 m	DiNardo and colleagues <sup>60</sup>
DAC	Vosaroxin	65	69	No	74%	NA	Daver and colleagues <sup>61</sup>
Decitabine LDAC	Cladribine	118	69	No	69%	13 m	Kadia and colleagues <sup>62</sup>
LDAC	Glasdegib	132	77	Yes	17.0% versus 2.3%*	8.8 versus 4.9 m	Cortes and colleagues <sup>63</sup>
LDAC	Volasertib	666	75	Yes	25.2% versus 16.8%*	4.8. versus 6.5 m*	Dohner and colleagues <sup>50</sup>
LDAC	Venetoclax	82	74	No	58% (62%)*	10 m (13.5 m)*	Wei and colleagues <sup>64</sup>
LDAC	Mylotarg	495	76	Yes	30% versus 17%	1-year OS 25% versus 27%**	Burnett and colleagues <sup>65</sup>

\*In the group of previously untreated patients.

\*\*for the experimental versus control arm respectively.

AML, acute myeloid leukemia; AZA, azacitidine; CR, complete response; CRi, incomplete hematological recovery; HMA, hypomethylating agent; LDAC, low-dose cytarabine; OS, overall survival.

trials. This may be due to the rigorous selection of patients in these trials and to the more intensive supportive care provided by highly specialized units.

Recently, however, several studies reported positive results that led to US FDA approvals of new compounds as first-line treatment of unfit patients with AML in combination with HMAs or LDAC.<sup>18</sup> A randomized phase II trial comparing the combination of glasdegib, an oral smoothed inhibitor, and LDAC with LDAC monotherapy demonstrated a higher CR rate (17.0% versus 2.3%, respectively;  $p < 0.05$ ) and superior overall patient survival (8.8 versus 4.9 months, respectively;  $p = 0.0004$ ).<sup>63</sup> Although positive, the results of this trial highlight the issue of the poor response

and outcome observed in the control arm. On 21 November 2018 the US FDA approved glasdegib in combination with LDAC for patients with newly diagnosed AML aged  $\geq 75$  years or with comorbidities.

Venetoclax is an oral inhibitor of the anti-apoptotic protein BCL-2. The two large phase I/II trials studied the effects of venetoclax in combination with either azacitidine or decitabine,<sup>60,66</sup> or LDAC in elderly patients with AML.<sup>64</sup> DiNardo and colleagues reported the administration of venetoclax doses of 400, 800, or 1200 mg daily in combination with either decitabine or azacitidine in 145 patients (median age 74 years) considered unfit for ICT. The final results showed that 67% of patients achieved CR/CRi with a median response

duration of 11.3 months and a median OS of 17.5 months. CR/CRi rates of 65% and 60% were seen in patients >75 years and in patients with poor-risk cytogenetics, respectively. In the venetoclax 400 mg + HMA cohort, the CR/CRi rate was 73% and median OS had not been reached.<sup>60</sup> These results compare favorably with HMA monotherapy, with results ranging from a CR rate of 18–28% and a median survival of 7–10 months.<sup>11,12</sup> A trial studied the combination of venetoclax (600 mg) with LDAC in 82 patients (median age 74 years). The CR/CRi rate was 54% and median survival was 10.1 months. Of note, in patients without previous HMA exposure, CR/CRi was achieved in 62% and median OS was 13.5 months.<sup>64</sup> A correlative study found that the combination of venetoclax with azacitidine disrupts the metabolic machinery driving energy metabolism and specifically targets leukemic stem cells. This eradication of leukemic stem cells may explain the regimen's efficacy.<sup>67</sup>

Based on these data, the US FDA approved venetoclax with azacitidine, decitabine, or LDAC for the treatment of patients with AML who are ineligible for intensive therapy. Phase III trials comparing these combination regimens with standard care [i.e. monotherapy with HMAs (ClinicalTrials.gov identifier: NCT02993523) or LDAC (ClinicalTrials.gov identifier: NCT03069352)] are currently ongoing and their conclusions are expected to validate the initial results. Nevertheless, these combination regimens are already considered as the new standard for the treatment of elderly unfit patients with AML and were included in the recent National Comprehensive Cancer Network guidelines.<sup>68</sup>

A noncomparative phase II trial of cladribine and LDAC while alternating decitabine administration was reported by Kadia and colleagues. Among 118 patients with AML ineligible for ICT, 68% patients achieved CR/CRi and the median OS was 13.8 months. It should also be noted that patients had a median age of 69 years, a median ECOG performance status of 1, and a quarter of them had received a transplant.<sup>62</sup> These characteristics are different from those of previously reported unfit patient populations, which typically included a median age of 74–75 years, ECOG performance status  $\geq 2$  in 25–30% of patients, and no transplants.<sup>11,12</sup> However, the response rate was comparable with that usually achieved with ICT regimens in fit patients

suggesting that 'intermediate-intensity' regimens may challenge ICT for appropriateness in fit patients. The encouraging results reported by Kadia and colleagues may also be explained by the favorable patient profile and may not be reproducible in less fit patients. It is likely that intensified low-intensity regimens such as these should not be offered to fragile patients because the addition of other agents with substantial hematological toxicity to an HMA or LDAC backbone may indeed cross the tolerance threshold of fragile patients.<sup>69</sup>

### Conclusion

Treatment decisions in the elderly patient population remain challenging due to our inability to formally, reproducibly, and accurately identify patients who are unfit for ICT. ICT continues to play an important role in the treatment of elderly patients with AML and represents an effective option for the growing number of allogeneic SCT candidates.<sup>70</sup> The recent development of novel and effective combination regimens based on HMAs or LDAC in combination with venetoclax challenges the current intensive *versus* nonintensive dilemma and raises the possibility of replacing ICT as standard care in the near future.<sup>71</sup>

It also opens new avenues for further therapeutic improvements based on the addition of targeted drugs such as FLT3 or IDH1 and IDH2 inhibitors, which are just a few notable examples among many other novel compounds. International cooperation and adaptive trial platforms will be essential to ensure both the accrual of sufficient patient numbers within specific molecular subgroups and sufficient flexibility in evaluating this multitude of new drugs in a timely manner.

### Funding

The author received no financial support for the research, authorship, and/or publication of this article.

### Conflict of interest statement

The author declares that there is no conflict of interest.

### ORCID iD

Norbert Vey  <https://orcid.org/0000-0001-7027-040X>

## References

- Juliusson G, Antunovic P, Derolf A, *et al.* Age and acute myeloid leukemia: real world data on decision to treat and outcomes from the Swedish acute leukemia registry. *Blood* 2009; 113: 4179–4187.
- Menzin J, Lang K, Earle CC, and colleagues The outcomes and costs of acute myeloid leukemia among the elderly. *Arch Intern Med* 2002; 162: 1597–1603.
- Vey N. Targeting age-related changes in the biology of acute myeloid leukemia: is the patient seeing the progress? *Interdiscip Top Gerontol* 2013; 38: 73–84.
- Taylor PR, Reid MM, Stark AN, and colleagues De novo acute myeloid leukaemia in patients over 55-years-old: a population-based study of incidence, treatment and outcome. Northern Region Haematology Group. *Leukemia* 1995; 9: 231–237.
- Juliusson G, Billstrom R, Gruber A, *et al.* Attitude towards remission induction for elderly patients with acute myeloid leukemia influences survival. *Leukemia* 2006; 20: 42–47.
- Aström M, Bodin L, Nilsson I, and colleagues Treatment, long-term outcome and prognostic variables in 214 unselected AML patients in Sweden. *Br J Cancer* 2000; 82: 1387–1392.
- Pigneux A, Bene MC, Salmi LR, *et al.* Improved survival by adding lomustine to conventional chemotherapy for elderly patients with AML without unfavorable cytogenetics: results of the LAM-SA 2007 FILO trial. *J Clin Oncol*. Epub ahead of print 2018. DOI: 10.1200/JCO.2018.78.7366.
- Lowenberg B, Ossenkoppele GJ, van Putten W, *et al.* High-dose daunorubicin in older patients with acute myeloid leukemia. *N Engl J Med* 2009; 361: 1235–1248.
- Castaigne S, Pautas C, Terre C, *et al.* Effect of gemtuzumab ozogamicin on survival of adult patients with de-novo acute myeloid leukaemia (ALFA-0701): a randomised, open-label, phase 3 study. *Lancet* 2012; 379: 1508–1516.
- Burnett AK, Milligan D, Prentice AG, *et al.* A comparison of low-dose cytarabine and hydroxyurea with or without all-trans retinoic acid for acute myeloid leukemia and high-risk myelodysplastic syndrome in patients not considered fit for intensive treatment. *Cancer* 2007; 109: 1114–1124.
- Dombret H, Seymour JF, Butrym A, *et al.* International phase 3 study of azacitidine vs conventional care regimens in older patients with newly diagnosed AML with >30% blasts. *Blood* 2015; 126: 291–299.
- Kantarjian HM, Thomas XG, Dmoszynska A, *et al.* Multicenter, randomized, open-label, phase III trial of decitabine versus patient choice, with physician advice, of either supportive care or low-dose cytarabine for the treatment of older patients with newly diagnosed acute myeloid leukemia. *J Clin Oncol* 2012; 30: 2670–2677.
- Muffy L, Pasquini MC, Martens M, *et al.* Increasing use of allogeneic hematopoietic cell transplantation in patients aged 70 years and older in the United States. *Blood* 2017; 130: 1156–1164.
- Dombret H and Itzykson R. How and when to decide between epigenetic therapy and chemotherapy in patients with AML. *Hematology Am Soc Hematol Educ Program* 2017; 2017: 45–53.
- Ferrara F, Barosi G, Venditti A, *et al.* Consensus-based definition of unfit to intensive and non-intensive chemotherapy in acute myeloid leukemia: a project of SIE, SIES and GITMO group on a new tool for therapy decision making. *Leukemia* 2013; 27: 997–999.
- Sorrow ML, Storer BE, Fathi AT, *et al.* Development and validation of a novel acute myeloid leukemia-composite model to estimate risks of mortality. *JAMA Oncol* 2017; 3: 1675–1682.
- Abel GA and Klepin HD. Frailty and the management of hematologic malignancies. *Blood* 2018; 131: 515–524.
- Tiong IS and Wei AH. New drugs creating new challenges in acute myeloid leukemia. *Genes Chromosomes Cancer* 2019; 58: 903–914.
- Gardin C, Chevret S, Pautas C, *et al.* Superior long-term outcome with idarubicin compared with high-dose daunorubicin in patients with acute myeloid leukemia age 50 years and older. *J Clin Oncol* 2013; 31: 321–327.
- Pluta A, Robak T, Wrzesien-Kus A, *et al.* Addition of cladribine to the standard induction treatment improves outcomes in a subset of elderly acute myeloid leukemia patients. Results of a randomized polish adult leukemia group (PALG) phase II trial. *Am J Hematol* 2017; 92: 359–366.
- Lancet JE, Uy GL, Cortes JE, *et al.* Final results of a phase III randomized trial of CPX-351 versus 7+3 in older patients with newly diagnosed high risk (secondary) AML. *J Clin Oncol* 2016; 34(Suppl): abstract 7000.




22. Walter RB, Othus M, Orlowski KF, *et al.* Unsatisfactory efficacy in randomized study of reduced-dose CPX-351 for medically less fit adults with newly diagnosed acute myeloid leukemia or other high-grade myeloid neoplasm. *Haematologica* 2018; 103: e106–e109.
23. Gardin C, Turlure P, Fagot T, *et al.* Postremission treatment of elderly patients with acute myeloid leukemia in first complete remission after intensive induction chemotherapy: results of the multicenter randomized Acute Leukemia French Association (ALFA) 9803 trial. *Blood* 2007; 109: 5129–35.
24. Stone RM, Berg DT, George SL, *et al.* Postremission therapy in older patients with de novo acute myeloid leukemia: a randomized trial comparing mitoxantrone and intermediate-dose cytarabine with standard-dose cytarabine. *Blood* 2001; 98: 548–553.
25. Huls G, Chitu DA, Havelange V, *et al.* Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. *Blood* 2019; 133: 1457–1464.
26. Stone RM, Mandrekar SJ, Sanford BL, *et al.* Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. *N Engl J Med* 2017; 377: 454–464.
27. Schlenk RF, Weber D, Fiedler W, *et al.* Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. *Blood* 2019; 133: 840–851.
28. Stein EM, DiNardo CD, Pollyea DA, *et al.* Enasidenib in mutant IDH2 relapsed or refractory acute myeloid leukemia. *Blood* 2017; 130: 722–731.
29. DiNardo CD, Stein EM, de Botton S, *et al.* Durable remissions with ivosidenib in IDH1-mutated relapsed or refractory AML. *N Engl J Med* 2018; 378: 2386–2398.
30. Stein EM, DiNardo CD, Fathi AT, *et al.* Ivosidenib or enasidenib combined with induction and consolidation chemotherapy in patients with newly diagnosed AML with an IDH1 or IDH2 mutation is safe, effective, and leads to MRD-negative complete remissions. *Blood* 2018; 132(Suppl. 1): 560.
31. Cruijnsen M, Lubbert M, Wijermans P, and colleagues Clinical results of hypomethylating agents in AML treatment. *J Clin Med* 2014; 4: 1–17.
32. Blum W, Garzon R, Klisovic RB, *et al.* Clinical response and miR-29b predictive significance in older AML patients treated with a 10-day schedule of decitabine. *Proc Natl Acad Sci USA* 2010; 107: 7473–7478.
33. Pleyer L, Burgstaller S, Girschikofsky M, *et al.* Azacitidine in 302 patients with WHO-defined acute myeloid leukemia: results from the Austrian azacitidine registry of the AGMT-study group. *Ann Hematol* 2014; 93: 1825–1838.
34. Thepot S, Itzykson R, Seegers V, *et al.* Azacitidine in untreated acute myeloid leukemia: a report on 149 patients. *Am J Hematol* 2014; 89: 410–416.
35. Bories P, Bertoli S, Berard E, *et al.* Intensive chemotherapy, azacitidine, or supportive care in older acute myeloid leukemia patients: an analysis from a regional healthcare network. *Am J Hematol* 2014; 89: E244–E252.
36. Seymour JF, Dohner H, Butrym A, *et al.* Azacitidine improves clinical outcomes in older patients with acute myeloid leukaemia with myelodysplasia-related changes compared with conventional care regimens. *BMC Cancer* 2017; 17: 852.
37. Wanquet A, Prebet T, Berthon C, *et al.* Azacitidine treatment for patients with myelodysplastic syndrome and acute myeloid leukemia with chromosome 3q abnormalities. *Am J Hematol* 2015; 90: 859–863.
38. Itzykson R, Kosmider O, Cluzeau T, *et al.* Impact of TET2 mutations on response rate to azacitidine in myelodysplastic syndromes and low blast count acute myeloid leukemias. *Leukemia* 2011; 25: 1147–1152.
39. Metzeler KH, Walker A, Geyer S, *et al.* DNMT3A mutations and response to the hypomethylating agent decitabine in acute myeloid leukemia. *Leukemia* 2012; 26: 1106–1107.
40. Welch JS, Petti AA, Miller CA, *et al.* TP53 and decitabine in acute myeloid leukemia and myelodysplastic syndromes. *N Engl J Med* 2016; 375: 2023–2036.
41. Issa JP, Garcia-Manero G, Giles FJ, *et al.* Phase 1 study of low-dose prolonged exposure schedules of the hypomethylating agent 5-aza-2'-deoxycytidine (decitabine) in hematopoietic malignancies. *Blood* 2004; 103: 1635–1640.
42. Roboz GJ, Kantarjian HM, Yee KWL, *et al.* Dose, schedule, safety, and efficacy of guadecitabine in relapsed or refractory acute myeloid leukemia. *Cancer* 2018; 124: 325–334.
43. Kantarjian HM, Roboz GJ, Kropf PL, *et al.* Guadecitabine (SGI-110) in treatment-naïve

- patients with acute myeloid leukaemia: phase 2 results from a multicentre, randomised, phase 1/2 trial. *Lancet Oncol* 2017; 18: 1317–1326.
44. Etienne A, Esterni B, Charbonnier A, *et al.* Comorbidity is an independent predictor of complete remission in elderly patients receiving induction chemotherapy for acute myeloid leukemia. *Cancer* 2007; 109: 1376–1383.
  45. Kantarjian H, Ravandi F, O'Brien S, *et al.* Intensive chemotherapy does not benefit most older patients (age 70 years or older) with acute myeloid leukemia. *Blood* 2010; 116: 4422–4429.
  46. Malfuson JV, Etienne A, Turlure P, *et al.* Risk factors and decision criteria for intensive chemotherapy in older patients with acute myeloid leukemia. *Haematologica* 2008; 93: 1806–1813.
  47. Sorror ML, Maris MB, Storb R, *et al.* Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood* 2005; 106: 2912–2919.
  48. Loh KP and Klepin HD. Geriatric assessment in older patients with acute myeloid leukemia. *Cancers* 2018; 10: pii: E225.
  49. Klepin HD, Geiger AM, Tooze JA, *et al.* Geriatric assessment predicts survival for older adults receiving induction chemotherapy for acute myelogenous leukemia. *Blood* 2013; 121: 4287–4294.
  50. Dohner H, Estey E, Grimwade D, *et al.* Diagnosis and management of AML in adults: 2017 ELN recommendations from an international expert panel. *Blood*. Epub ahead of print 28 November 2016. DOI: 10.1182/blood-2016-08-733196.
  51. Stahl M, Lu BY, Kim TK, and colleagues Novel therapies for acute myeloid leukemia: are we finally breaking the deadlock? *Target Oncol* 2017; 12: 413–447.
  52. Garcia-Manero G, Assouline S, Cortes J, *et al.* Phase 1 study of the oral isotype specific histone deacetylase inhibitor MGCD0103 in leukemia. *Blood* 2008; 112: 981–989.
  53. Gore SD. In vitro basis for treatment with hypomethylating agents and histone deacetylase inhibitors: can epigenetic changes be used to monitor treatment? *Leuk Res* 2009; 33(Suppl. 2): S2–S6.
  54. Daver N, Boddu P, Garcia-Manero G, *et al.* Hypomethylating agents in combination with immune checkpoint inhibitors in acute myeloid leukemia and myelodysplastic syndromes. *Leukemia* 2018; 32: 1094–1105.
  55. Kung Sutherland MS, Walter RB, Jeffrey SC, *et al.* SGN-CD33A: a novel CD33-targeting antibody-drug conjugate using a pyrrolobenzodiazepine dimer is active in models of drug-resistant AML. *Blood* 2013; 122: 1455–1463.
  56. Fathi AT, Erba HP, Lancet JE, *et al.* A phase 1 trial of vadastuximab talirine combined with hypomethylating agents in patients with CD33-positive AML. *Blood* 2018; 132: 1125–1133.
  57. Dohner H, Lubbert M, Fiedler W, *et al.* Randomized, phase 2 trial of low-dose cytarabine with or without volasertib in AML patients not suitable for induction therapy. *Blood* 2014; 124: 1426–1433.
  58. Swords RT, Coutre S, Maris MB, *et al.* Pevonedistat, a first-in-class NEDD8-activating enzyme inhibitor, combined with azacitidine in patients with AML. *Blood* 2018; 131: 1415–1424.
  59. Garcia-Manero G, Abaza Y, Takahashi K, *et al.* Pracinostat plus azacitidine in older patients with newly diagnosed acute myeloid leukemia: results of a phase 2 study. *Blood Adv* 2019; 3: 508–518.
  60. DiNardo CD, Pratz K, Pullarkat V, *et al.* Venetoclax combined with decitabine or azacitidine in treatment-naïve, elderly patients with acute myeloid leukemia. *Blood* 2019; 133: 7–17.
  61. Daver N, Kantarjian H, Garcia-Manero G, *et al.* Vosaroxin in combination with decitabine in newly diagnosed older patients with acute myeloid leukemia or high-risk myelodysplastic syndrome. *Haematologica* 2017; 102: 1709–1717.
  62. Kadia TM, Cortes J, Ravandi F, *et al.* Cladribine and low-dose cytarabine alternating with decitabine as front-line therapy for elderly patients with acute myeloid leukaemia: a phase 2 single-arm trial. *Lancet Haematol* 2018; 5: e411–e421.
  63. Cortes JE, Heidel FH, Hellmann A, *et al.* Randomized comparison of low dose cytarabine with or without glasdegib in patients with newly diagnosed acute myeloid leukemia or high-risk myelodysplastic syndrome. *Leukemia*. Epub ahead of print 16 December 2018. DOI: 10.1038/s41375-018-0312-9.
  64. Wei AH, Strickland SA, Hou JZ, *et al.* Venetoclax combined with low-dose cytarabine for previously untreated patients with acute myeloid leukemia: results from a phase Ib/II study. *J Clin Oncol* 2019; 37: 1277–1284.
  65. Burnett AK, Hills RK, Hunter AE, *et al.* The addition of gemtuzumab ozogamicin to low-dose

- Ara-C improves remission rate but does not significantly prolong survival in older patients with acute myeloid leukaemia: results from the LRF AML14 and NCRI AML16 pick-a-winner comparison. *Leukemia* 2013; 27: 75–81.
66. DiNardo CD, Pratz KW, Letai A, *et al.* Safety and preliminary efficacy of venetoclax with decitabine or azacitidine in elderly patients with previously untreated acute myeloid leukaemia: a non-randomised, open-label, phase 1b study. *Lancet Oncol* 2018; 19: 216–228.
67. Pollyea DA, Stevens BM, Jones CL, *et al.* Venetoclax with azacitidine disrupts energy metabolism and targets leukemia stem cells in patients with acute myeloid leukemia. *Nat Med* 2018; 24: 1859–1866.
68. Tallman MS, Wang ES, Altman JK, *et al.* Acute myeloid leukemia, version 3.2019, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw* 2019; 17: 721–749.
69. Vey N. Blurring lines between treatment intensity and patient fitness in elderly people with AML. *Lancet Haematol* 2018; 5: e383–e384.
70. Michaelis LC. Cytotoxic therapy in acute myeloid leukemia: not quite dead yet. *Hematology Am Soc Hematol Educ Program* 2018; 2018: 51–62.
71. Wei AH and Tiong IS. Midostaurin, enasidenib, CPX-351, gemtuzumab ozogamicin, and venetoclax bring new hope to AML. *Blood* 2017; 130: 2469–2474.

Visit SAGE journals online  
[journals.sagepub.com/  
 home/tah](http://journals.sagepub.com/home/tah)

 SAGE journals