REVIEW ARTICLE

Update on current treatments for adult acute myeloid leukemia: to treat acute myeloid leukemia intensively or non-intensively? That is the question

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Abstract

For several decades, the treatment for acute myeloid leukemia (AML) has been a dichotomous choice between intensive chemotherapy strategies with curative intent and non-intensive options including supportive care. Patients' age and fitness, as well as comorbidities, primarily influenced this choice. However, the therapeutic armamentarium is evolving, so that there are highly effective and increasingly specific drugs, fitting the mutational profile of a patient's leukemia. There is now a spectrum of treatment options that are less intense and can be administered in an outpatient setting and to a substantial extent are equally or even more effective than standard intensive therapy. We are, therefore, witnessing a radical change in the treatment landscape of AML. In this review, we examine the current treatment options for patients with AML, considering the molecular spectrum of the disease on the background of patient-related factors.

Introduction

Acute myeloid leukemia (AML) is the most common acute leukemia in adults with an incidence ranging from 2.0 per 100,000 men and women per year in Korea[1] to 4.3 per 100,000 people per year in the USA[2] with a median age at diagnosis ranging in western countries between 65 and 72 years.[3-5] Over the last years the incidence has remained stable in younger patients but has increased significantly in patients aged over 75 years.[5-7] This phenomenon has not yet been fully explained, but may be related to various factors, including longer life expectancy, increasing awareness, improving diagnostic sensitivity, better reporting and recording of new cases, and an increase of exposure to risk factors.[8] Treatment approaches have been and are influenced by patients' features such as age, comorbidities, and Eastern Cooperative Oncology Group performance status. However, determining the molecular profile of AML is essential as it has become a major prognostic factor, but even more importantly the pivotal predictive parameter for selecting the most appropriate treatment for an individual case.[9-13]

Risk stratification guidelines combining information on cytogenetic abnormalities and gene mutations have been widely used to predict the prognosis of AML patients and to select risk-adapted post-remission therapy, in particular with regards to allogeneic hematopoietic cell transplantation (allo-HCT).[14,15] Mutations in genes such as nucleophosmin-1 (*NPM1*), FMS-related tyrosine kinase 3 (*FLT3*), and CCAAT/enhancer-binding protein alpha (*CEBPA*), somatic mutations in isocitrate dehydrogenase 1 and 2 (*IDH1/2*), *RUNX1*, *TP53* and *KMT2A* mutations as well as the presence of either t(8;21)(q22;q22)/*RUNX1-RUNX1T1* or inv(16) (p13q22)/t(16;16)(p13q22)/*CBFB-MYH11* influence the therapeutic approach to patients with newly diagnosed AML[9] and documenting their presence has entered clinical routine.[15,16] Furthermore, genetic mutations have played and still play an essential role in deciding the type and intensity of induction and post-induction therapy.[14,17] However, there are significant barriers to the translation of the molecular characteristics of AML into precise clinical action and ultimately most patients will receive standard-of-care treatments.[14] Nevertheless, we currently find ourselves in an era of rapid transition from the use of the standard "7+3" chemotherapy to precise therapeutic strategies based on specific disease characteristics as well as an individual patient's characteristics. In this review, we examine the current treatment options for pa-

tients with AML, considering the molecular findings of the disease as well as the age and fitness of the patient.

Intensive *versus* non-intensive therapy

Non-intensive therapies are being increasingly used in patients above the age of 65 years because of concerns about such patients' ability to tolerate intensive chemotherapy regimens.[18] However, the risk-benefit ratio associated with intensive *versus* non-intensive therapies in elderly patients in the era of new targeted agents remains unknown as upfront randomized comparisons are lacking. Furthermore, as conventional induction therapies such as the "7+3" regimen have been upgraded with the introduction of new agents, including venetoclax, midostaurin, gilteritinib, quizartinib, gemtuzumab ozogamicin (GO), ivosidenib and enasidenib as well as CPX351, it may be difficult to define the standard in a chemotherapy arm of a future randomized study. Regarding non-intensive therapy, the combination of hypomethylating agents and venetoclax has revolutionized the therapeutic landscape of elderly patients with AML.[19] Currently recruiting studies are evaluating the feasibility of non-intensive regimens achieving long-lasting molecular complete remissions (CR) in older as well as younger patients. As an example, VINCENT (EudraCT-No 2021-003248-26) is a phase II trial evaluating induction and consolidation therapy with azacitidine and venetoclax (aza-ven) *versus* standard of care, defined as intensive "7+3" induction therapy with GO in patients fit for intensive induction therapy with *NPM1*-mutated AML according to Schlenk *et al.*[20] Furthermore, for patients aged between 60 and 75 years in whom allo-HCT is intended, a single-arm, phase II study (NCT04476199) of decitabine plus venetoclax is evaluating this therapy combination as a bridge to allo-HCT. A recent retrospective study aiming to predict the optimal type of conditioning and maintenance therapy to reduce the risk of relapse in older patients undergoing allo-HCT indicated that relapse risk as well as the risk of measurable residual disease (MRD) and treatment-related toxicity can be predicted from baseline genetic characteristics.[21]

A multicenter, retrospective, cohort study of patients transplanted in first CR after either intensive induction therapy (n=24) or non-intensive therapy with aza-ven (n=24) showed that those treated with intensive induction therapy achieved inferior results compared to those treated non-intensively with regard to both 12-month non-relapse mortality (19.1% *vs*. 11.8%, respectively) and overall survival (OS) (54% *vs*. 70%, respectively).[22] Further comparative retrospective evaluations in patients with newly diagnosed AML treated with aza-ven (n=143) or intensive chemotherapy (n=149) showed comparable or even superior overall response rates (CR, CR with incomplete recovery of blood counts [CRi], and morphological leukemia-free state) with aza-ven (76.9%) than with intensive chemotherapy (70.5%) but an inferior median OS (483 days with aza-ven *vs*. 884 days with intensive chemotherapy; *P*=0.002).[23] Variables that favored response to aza-ven over intensive chemotherapy included older age (odds ratio [OR]=2.79, 95% confidence interval [95% CI]: 1.18-6.59), secondary AML (OR=2.36, 95% CI: 1.0-5-3), and *RUNX1* mutation (OR=5.4, 95% CI: 1.1-26.9). Contrary to our expectations, in the aza-ven subgroup analysis, *RUNX1* mutation was not prognostic for either response or OS.[23] Based on these findings, *RUNX1* might be a useful variable to help guide clinical decision-making between aza-ven and intensive chemotherapy. However, the clinical application of conclusions from retrospective analyses are fundamentally limited, so prospective studies are needed to support these observations. In line with these findings, an interim analysis of an ongoing phase II clinical trial (NCT04752527) studying decitabine plus venetoclax for young adults with newly diagnosed adverse-risk AML (according to the European LeukemiaNet [ELN] classification) revealed good clinical activity with even better results compared to those of historical controls given intensive chemotherapy (CR with partial hematologic recovery [CRh]: 64.3% *vs*. 38.3%, respectively).[24]

ASXL1 has also been described as a potential marker for improved response to venetoclax based on non-intensive therapy in previous studies.[25-28] Moreover, in one of these studies, *ASXL1* mutation was found to have a favorable impact on the achievement of CR/CRi independently of the presence of a concomitant *TP53* mutation.[25]

On the other hand, the diagnosis of monocytic leukemia was found to favor treatment with intensive chemotherapy compared to aza-ven in the already mentioned retrospective study (CR achievement: OR=0.08, 95% CI: 0.01-0.5).[23] In line with this finding, in a cohort study of 100 patients with AML, the presence of a monocytic phenotype was associated with refractoriness to aza-ven (OR=18.285, 95% CI: 4.701-71.129).[29] The underlying genetic events that may drive this process are not, as yet, well characterized.

Venetoclax has also been combined with intensive regimens in recent studies. In a prospective cohort study, venetoxclax was added to fludarabine, cytarabine, granulocyte colony-stimulating factor, and idarubicin (FLAG-IDA). Venetoclax and FLAG-IDA were administered to 45 patients with newly diagnosed AML. The authors reported that 89% (n=40/45) of patients attained a composite CR and 93% of these responding patients achieved a deep MRD-negative remission following one cycle of therapy. Even patients with ELN adverse-risk AML without *TP53* mutations (n=15) showed favorable survival outcomes. The 12- and estimated 24-month OS rates were 92% and 76%, respectively.[30] In the CAVEAT trial, patients with newly diagnosed AML treated with venetoclax combined with cytarabine and idarubicin showed a similar response rate of 97% and a median OS of 31 months.[31] Venetoclax was also combined

with cytarabine and daunorubicin in a recent clinical study. This combination led to similar response rates in patients with *de novo* AML (n=33) with a composite CR rate of 91% after one cycle of the treatment. Of the 30 patients who reached CR, 29 (97%) did not have detectable MRD after one cycle of therapy.[32]

There is a tendency to treat older patients with less intensive therapies based on the assumptions that they will neither tolerate nor benefit from intensive therapies.[33] Sorror *et al.* published several tools to support the decision between intensive and non-intensive therapy in a clinical context[18,34] and they seem to be as important as other risk factors such as the molecular profile of disease.[18] These tools are based on retrospective and prospective data suggesting that elderly patients with AML do not necessarily benefit from less intensive therapies, with regard to survival outcomes or quality of life, regardless of the degree of their medical unfitness as captured by a validated model. Although these tools are being increasingly used in clinical practice, a patient's fitness still remains a subjective determination for many clinicians. With the approval of newer AML treatment options, including non-intensive therapy with the potential to induce CR, the role of a patient's fitness in treatment selection has become yet more complex. Clinicians must now determine not only whether a newly diagnosed patient with AML is fit to withstand intensive induction chemotherapy but also whether induction chemotherapy is the optimal choice, given the patient's disease features and availability of newer, less intensive treatment options. During the COVID-19 pandemic, physicians have been forced to rethink the indications for intensive chemotherapy in young, fit patients. A recent study addressed this issue, looking at responses in patients fit for intensive chemotherapy who were treated with aza-ven or low-dose cytarabine plus venetoclax.[35] In 301 patients, with a median age of 72 years (range, 34-90), the composite CR rate was 70% and, with a median follow-up of 8.2 months, the median OS was 12.8 months (95% CI: 10.9 months - not reached). The mutational landscape of this cohort resembled that expected in the real world and prognostic molecular and clinical factors support findings from previous studies in older patients.[19,36,37] These data support the idea of using non-intensive regimens for young and old patients with AML who are actually fit for intensive chemotherapy (Table 1) and, more importantly, they support the adoption of venetoclax regimens to treat patients with AML at a time of critically constrained resources, since such patients spent significantly fewer days in hospital (15 days *vs.* 41 days).[38] Similar results were seen in another real-world cohort.[39]

Recently, decitabine, as monotherapy for 5 to 10 days, was compared to daunorubicin and cytarabine (the "7+3" regimen), followed by one to three additional chemotherapy cycles in patients with newly diagnosed AML above the age of 60 years. The CR/CRi rate was 48% with decitabine and 61% with intensive chemotherapy. As part of the protocol, 122 patients (40%, 30 of them not in CR/CRi) in the decitabine arm, and 118 patients (39%, 11 of them not in CR/CRi) in the intensive chemotherapy arm underwent allo-HCT. The median OS was not significantly different between the groups treated with decitabine or intensive chemotherapy (15 *vs.* 18 months, respectively; HR=1.04, 95% CI: 0.86-1.26). Interestingly, significantly fewer grade 3-5 adverse events were seen in patients treated with decitabine than in those treated with intensive chemotherapy.[40] The potential benefits of intensive *versus* non-intensive therapy are presented in Table 2.

Targeted therapy in adults fit for intensive chemotherapy

FLT3 inhibitors

Mutations in *FLT3* are among the most frequent genetic aberrations in patients with AML, with the frequency being

Table 1. Potential predictive markers to favor intensive or non-intensive therapy for induction of remission.

Marker	Favored therapy	Evidence source	References
Age ≥ 65 years	Non-intensive	Cohort study	19, 23
ELN adverse risk	Non-intensive	Cohort study	23
Mutated *RUNX1*	Non-intensive	Cohort study	23
Secondary AML	Non-intensive	Cohort study	23
FAB-M5 morphology	Intensive	Cohort study	23
ASXL1	Non-intensive	Cohort study	25-28
FLT3	Intensive	Randomized clinical trial	49-53

ELN: European LeukemiaNet; *RUNX1*: Runt-related transcription factor 1; AML: acute myeloid leukemia; FAB: French American British; *ASXL1*: Additional sex combs-like 1; *FLT3*: Fms-related receptor tyrosine kinase 3.

Table 2. Potential benefits of intensive *versus* non-intensive therapy.

Intensive chemotherapy ± targeted therapies	Non-intensive therapy ± targeted therapies	Evidence source	References
Combination with venetoclax produced greater molecular remission in fit, *de novo* AML patients		Phase I-II clinical trials	30-32
	Combination with venetoclax led to improvements in CR in patients with poor-risk cytogenetics	Phase III clinical trials	23, 25-28
	Fewer infectious complications	Cohort studies	38, 39, 40
	Better tolerability for older patients	Phase III clinical trials	36, 37
	Fewer days in hospital	Cohort studies	38, 39
Combination with FLT3 inhibitors was proven efficacious		Phase II and III clinical trials	49-53
Widely evaluated and broadly accepted		Clinical guidelines	16
Addition of GO led to lower relapse rate in younger patients			20, 64
Combination with IDH inhibitors was proven efficacious		Phase I and phase III clinical trials	59-62

CR: complete remission; FLT3: Fms-related receptor tyrosine kinase 3; GO: gemtuzumab ozogamicin; IDH: isocitrate dehydrogenase.

higher in younger patients than in older ones.[3] There are two main types of *FLT3* mutations: (i) internal tandem duplications (ITD), occurring in 10-25% of patients and resulting in the duplication of nucleotide sequences with differing lengths and insertion sites, are associated with inferior clinical outcomes, in particular in patients with higher allelic ratios[41-44] and (ii) single-nucleotide variants in the tyrosine kinase domain (TKD), occurring in 5-10% of patients; these are associated with a more favorable prognosis, in particular when occurring together with *NPM1* mutations or core-binding factor AML.[43,45]

There is a significant unmet medical need to improve the duration of response in patients with newly diagnosed *FLT3*-ITD-positive AML,[46] and so the clinical development of FLT3 inhibitors has been one of the most active fields in precision medicine for AML.[47] Type 1 inhibitors, such as midostaurin, gilteritinib and crenolanib are less selective tyrosine kinase inhibitors, whereas the type 2 FLT3 inhibitor quizartinib is highly selective for FLT3 and particularly *FLT3*-ITD.[48,49] Midostaurin is currently the only tyrosine kinase inhibitor approved for use in patients with *FLT3*-mutated newly diagnosed AML that has demonstrated superior results compared to standard intensive therapy for all survival endpoints, including OS.[50] In contrast to the Food and Drug Administration (FDA), the European Medicines Agency (EMA) not only approved midostaurin for the treatment of newly diagnosed AML patients with an activating *FLT3* mutation, including *FLT3*-ITD and *FLT3*-TKD mutations, in combination with intensive induction and consolidation therapy but also as 1-year maintenance therapy. Supported by a phase II follow-up study of the RATIFY trial, the approval was not age-restricted.[51] However, based on published data,[50,51] roughly one-quarter of patients treated with midostaurin in combination with intensive induction therapy were refractory and the relapse rate at 2 years exceeded 40% despite consolidation and maintenance therapy with midostaurin. Thus, new treatment options are urgently needed.

A recent comparison of patients treated with midostaurin in the single-arm phase-II AMLSG 16-10 trial with a historical cohort of 415 patients treated on five prior AMLSG trials and with patients (18-59 years old) treated on the placebo arm of the RATIFY trial revealed better event-free survival in patients treated within the AMLSG 16-10 trial than in the controls from other AMLSG trials (HR=0.55; P<0.001) as well as the younger patients (<60 years) in the placebo arm of the RATIFY trial (HR=0.71; P=0.005). The treatment effect of midostaurin remained significant in the sensitivity analyses including allo-HCT as a time-dependent covariate as well as a competing event. It should be noted that in the multivariate analysis for event-free survival, allo-HCT in first CR

or CRi as a time-dependent covariate was significantly associated with a better survival (HR=0.49; 95% CI: 0.34-0.69).[52] The same was observed in the RATIFY study and in a recent exploratory analysis of the trial there was particularly good efficacy of induction therapy with midostaurin followed by allo-HCT in first CR in patients with *NPM1* wild-type or core-binding factor-negative AML.[45,51] In the AMLSG 16-10 trial the median OS was 22.7 months for older patients and 57.3 months for younger patients. In the multivariate analysis, the improvement in OS of elderly patients treated with midostaurin (HR=0.47; *P*<0.001) was even more pronounced than that in younger patients (HR=0.59; *P*<0.001). The frequency of serious adverse events was significantly higher in older patients than in younger ones, with the most common ones in older patients being vascular complications (21 *vs*. 13%, respectively; *P*=0.04) and metabolism and nutrition disorders (38 *vs*. 23%, respectively; *P*=0.003).[52]

Quizartinib is a type 2 FLT3 inhibitor exhibiting highly potent and selective, but reversible, inhibition of FLT3. It inhibits FLT3 kinase activity by preventing autophosphorylation of the receptor, blocking *FLT3*-ITD-dependent cell proliferation, and enhancing differentiation of *FLT3*-ITD-mutated stem cells into mature circulating cells.[47] Data from the phase III QuANTUM-First study, a randomized, double-blinded, placebo-controlled study evaluating quizartinib in combination with induction and consolidation chemotherapy and as 3-year continuation monotherapy in patients (aged 18-75 years) with newly diagnosed *FLT3*-ITD-positive AML, showed a statistically significant and clinically meaningful improvement in OS when compared with that in patients who received standard treatment and placebo.[53] With a median follow-up of 39.2 months, the median OS in the quizartinib arm was significantly longer than that in the placebo arm of the study (31.9 *vs*. 15.1 months, respectively; HR=0.776, two-sided *P*=0.0324). The OS rates at 24 months were 54.7% and 44.7% in the quizartinib and placebo arms, respectively. When censoring for allo-HCT, there was still a strong effect in favor of quizartinib (HR=0.752, 95% CI: 0.562-1.008; *P*=0.055) with a median OS of 20.8 months in the quizartinib arm and 12.9 months in the placebo arm. This suggests that, in contrast to midostaurin, the strong FLT3 inhibitor quizartinib is very efficacious independently of allo-HCT. The efficacy of quizartinib is based on a tendency to a better CR/CRi rate (quizartinib, 71.6%; placebo, 64.9%; *P*=0.0912) and a significantly better relapse-free survival (HR=0.613, 95% CI: 0.444-0.845) for subjects achieving CR during induction, with a median relapse-free survival of 39.3 months in the quizartinib arm compared to 13.6 months in the placebo arm. Of note, subgroup analyses for OS showed that patients with a higher variant allele frequency (>50%) treated with quizartinib had a significantly greater therapeutic benefit, with a risk reduction of roughly 47% (HR=0.526, 95% CI: 0.29-0.955) compared to patients treated with placebo which again contrasts with the midostaurin data with a risk reduction of only 20% (HR=0.80, 95% CI: 0.6-1.11) in these high-risk patients.[50] Furthermore, patients with a high allelic *FLT3*-ITD ratio treated with midostaurin in the AMLSG 16-10 trial did not show a significant improvement in OS compared to patients in the historical cohort treated with chemotherapy alone (HR=1.20, 95% CI: 0.98-1.47; *P*=0.082).[52]

Treatment-emergent serious adverse events and adverse events in the QuANTUM-First trial were significantly more frequent in the subgroup of patients older than 65 years, thus, special measures should be taken when treating older patients with quizartinib and intensive chemotherapy regimens.[53]

Gilteritinib, a type 1, oral FLT3 inhibitor with activity against both *FLT3* mutation subtypes (ITD and TKD) and weak activity against c-Kit was evaluated in a phase I study including newly diagnosed patients with *FLT3*-ITD mutated AML. Patients received induction therapy with gilteritinib plus the "7+3" regimen and high-dose cytarabine consolidation chemotherapy, as well as single-agent maintenance therapy. In an interim analysis of 80 patients with a median age of 59.0 years, the median follow-up for OS was 35.8 months. Serious treatment-related adverse events and adverse events leading to discontinuation of gilteritinib occurred in 12.7%. Among patients within the expansion cohort receiving the final dosage of gilteritinib, the investigator-reported CR/CRi rate was 81.6%. In *FLT3*-mutated patients who achieved CR or CRi in any dose group, the median duration of the composite CR and disease-free survival were 14.1 and 15.3 months, respectively.[54] Based on these results, a study of gilteritinib *versus* midostaurin in combination with induction and consolidation therapy followed by 1-year maintenance in patients with newly diagnosed AML or myelodysplastic syndromes with excess blasts-2 and with *FLT3* mutations eligible for intensive chemotherapy (HOVON 156 AML, NCT04027309) has been initiated. Gilteritinib is also being compared to midostaurin in a randomized, open-label, multicenter phase II study in combination with cytarabine and daunorubicin in newly diagnosed *FLT3*-mutated AML patients aged 18-65.[55]

Furthermore, results from two large, randomized studies testing the efficacy of gilteritinib maintenance therapy, one following consolidation therapy (NCT02927262) and the other after allo-HCT (NCT02997202), are currently awaited and should provide more definitive guidance on the use of this tyrosine kinase inhibitor in maintenance therapy.

IDH inhibitors

Isocitrate dehydrogenase 1 (IDH1) and IDH2 are $NADP^+$-dependent enzymes that catalyze the oxidative decarboxylation of isocitrate to α-ketoglutarate and are thus key components of the Krebs cycle.[56] Somatic gain-of-func-

tion mutations in *IDH1* or *IDH2* are found in approximately 20% of patients with newly diagnosed AML.[56-58] Enasidenib is an oral, selective inhibitor of mutated *IDH2*, approved by the FDA for the treatment of adult patients with relapsed or refractory *IDH2*-mutated AML. Its approval was based on the results of a phase I/II trial including 176 patients.[59] The overall response rate was 40.3% (CR, 27%).

Ivosidenib is an oral small molecule inhibitor of mutated *IDH1* approved by the FDA for the treatment of adult patients with relapsed or refractory AML with mutated *IDH1*. The approval was based on results of an open-label, phase I dose-escalation and dose-expansion study involving 258 adult patients with *IDH1*-mutated AML. The primary efficacy population consisted of 125 patients and the overall response rate ranged from 39.1% (95% CI: 31.9-46.7%) in relapsed/refractory AML to 55.9% (95% CI: 37.9-72.8%) in newly diagnosed AML.[60]

In a recent open-label, multicenter, phase I study (NCT02632708), patients with newly diagnosed mutated *IDH1* or *IDH2* AML (n=153), were treated with induction therapy ("7+3") in combination with either ivosidenib (n=60) or enasidenib (n=93). CR/CR with incomplete neutrophil or platelet recovery (CR/CRi/CRp) rates were 72% and 63%, respectively. Among patients with a best overall response of CR/CRi/CRp, of the 41 patients who received ivosidenib, 16 (39%) achieved clearance of the *IDH1* mutation, as determined by digital polymerase chain reaction, and 16 of 20 did not have MRD by multiparameter flow cytometry. Likewise, 15/64 (23%) patients receiving enasidenib showed *IDH2* mutation clearance and 10/16 (63%) patients became negative for MRD by multiparameter flow cytometry. In the older study population (median age 63 years), the treatment was well tolerated, and the first clinical results were encouraging.[61,62] The efficacy of these two compounds is being further evaluated in the ongoing HOVON150 AML randomized phase III trial (NCT03839771). Results of studies of IDH inhibitors with azacitidine were also encouraging, although the composite CR rate (53%) was lower than that seen with intensive therapy.[63]

Anti-CD33

GO is a humanized immunoglobulin G4 antibody (hP67.6) directed against CD33 and conjugated via a hydrolyzable linker to the DNA toxin calicheamicin. GO/CD33 complexes are internalized into lysosomes, releasing calicheamicin and promoting single- and double-strand DNA breaks and cellular death. Based mainly on the results of the ALFA-0701 study in newly diagnosed patients, GO was reapproved for use in AML patients, after it had been withdrawn from the market in June 2010 by Pfizer. In the ALFA 0701 study, patients in the GO arm had significantly improved median event-free (19.6 *vs*. 11.9 months; *P*=0.00018) and OS (34 *vs*. 19.2 months; *P*=0.046).[64] Although the difference in OS was no longer statistically significant when updated data were analyzed,[65] the trend to a longer OS observed in the GO arm of ALFA-0701 is consistent with the results found in a meta-analysis of individual patients' data that showed a significant improvement in OS in patients treated with GO.[66] In the AMLSG 09-09 study, 588 adult patients with newly diagnosed *NPM1*-mutated AML were randomly assigned to standard arm (n=296) with induction therapy consisting of idarubicin, cytarabine, etoposide, and all-*trans* retinoic acid or the GO arm (n=292) with GO as an adjunct to therapy given to the patients in the standard arm.[20] The early primary endpoint, event-free survival, was not significantly different between the two arms (HR=0.83, 95% CI: 0.65-1.04; *P*=0.10), mainly because of a significantly higher infection-triggered early death rate during induction therapy in the GO arm (10.3% *vs*. 5.7% in the standard arm; *P*=0.05). However, the addition of GO resulted in a significant and clinically meaningful reduction in the cumulative incidence of relapse (HR=0.66, 95% CI: 0.49-0.88; *P*=0.005) leading to a strong recommendation in current guidelines to add GO to standard induction therapy in *NPM1*-mutated AML.[14,67] In a companion study evaluating *NPM1* MRD during the trial, overall, the addition of GO significantly reduced MRD levels at all time-points compared to those in the standard arm.[68] However, despite achieving *NPM1* MRD negativity after consolidation therapy, one-quarter of the patients still relapsed within 4 years.[20] This indicates that further efforts need to be invested in refining MRD assessment and determining its relevance, in particular in the evaluation of maintenance therapy. The final results from the AMLSG 0909 study will further clarify the role of GO as an adjunct to intensive induction therapy; however, it is already known that GO in this setting has a broad toxicity spectrum, especially in older patients. Indeed the older population had no benefit from the addition of GO in any of the response or survival endpoints, whereas the rates of CR/CRi, event-free survival and cumulative incidence of relapse were similar between treatment arms. Furthermore, the 30- and 60-day mortality rates were higher in the GO arm.[69]

NPM1

Nucleophosmin-1 (NPM1) is a nuclear phosphoprotein involved in epigenetic cellular regulation through nuclear-cytoplasmic shuttling.[70-72] Mutations in *NPM1* occur in 30% of patients with AML and are associated with a favorable response to standard intensive chemotherapy, with both high CR rates and good OS.[73] As already mentioned, patients harboring mutations in the *NPM1* gene respond favorably to intensive induction with the "7+3" regimen plus GO, with CR rates around 85% and 5-year OS around 40-50%.[20] of note, impressive responses have also been observed when patients are treated with non-intensive therapy (aza-ven). In the VIALE-A phase III study (n=27) the

overall response rate was 93% and the 2-year OS was 75% for patients harboring a *NPM1* mutation.[36,37,74] Early mortality (30 days) in this cohort of elderly unfit patients was only 3%.

Furthermore, there are reports about patients not achieving molecular remission after consolidation therapy who had rapid elimination of *NPM1* MRD when azacitidine or low-dose cytarabine and venetoclax were administered as bridging therapy to allo-HCT.[75] All these data raise the possibility that the non-intensive combination of aza-ven may be equivalent or even superior to intensive chemotherapy in terms of clinical outcome in patients with *NPM1*-mutated AML which is the basis of the above-mentioned VINCENT trial (EudraCT-No 2021-003248-26).

Secondary acute myeloid leukemia

CPX-351 is a liposomal encapsulation of cytarabine/daunorubicin in a 5:1 molar ratio. Its use was approved based on the results of a randomized study in patients with therapy-associated AML, a history of myelodysplastic syndrome, AML with a history of chronic myelomonocytic leukemia, or *de novo* AML with myelodysplasia-related cytogenetic changes. CPX-351 was compared to standard induction and consolidation therapy in older patients (60-75 years).[76] The study showed that patients receiving CPX-351 had a higher CR rate (47.7% *vs*. 33.3%; *P*=0.016) and better OS (median, 9.56 *vs*. 5.95 months; *P*=0.005) compared to those given standard induction and consolidation therapy.[76] This study included 63 patients (30 patients in the CPX-351 and 33 in the standard arm) with therapy-related AML. The definition of therapy-related AML was AML in patients who had previously received alkylating agents, ionizing radiation therapy, treatment with topoisomerase II inhibitors, antimetabolites or antitubulin agents.

A recent retrospective study compared survival outcomes of patients treated with CPX-351 (n=219) or aza-ven (n=440).[38,77] Patients with therapy-related AML (n=17 in each arm) were also included. For all patients, baseline covariates showed that those receiving aza-ven were older (median age, 75 *vs*. 65 years), mainly had *de novo* AML (52% *vs*. 29%) and were treated in the community rather than in academic centers (66% *vs*. 52%). All other baseline covariates, including cytogenetic risk according to the ELN classification, the presence of prognostic mutations (*TP53*, *ASXL1*, *RUNX1*), or relevant comorbidities were not different between the treatment arms. The median OS was 13 months in patients treated with CPX-351 and 11 months for those given aza-ven (HR=0.87, 95% CI: 0.70-1.07; *P*=0.184). In the multivariate analysis considering complete cases only (n=133), the type of therapy (CPX-351 *vs*. aza-ven did not affect OS (*P*=0.73). In subgroup analysis, none of the AML types (*de novo*, secondary, or therapy-related AML) benefited more from one or the other therapy. Regarding safety outcomes, early mortality was similar. However, the rates of documented febrile neutropenia as well as culture-positive infections were significantly higher in patients treated with CPX-351 (90% *vs*. 53% and 67% *vs*. 36%, respectively; both *P*<0.000005). Length of hospital stay, including any admission prior to the next cycle of therapy, was 41 days in patients treated with CPX-351 compared to 15 days in patients treated with aza-ven (*P*<0.000005). These retrospective data suggest that aza-ven treatment may be equally effective as or at least not inferior to CPX-351, and is associated with significantly fewer infectious complications and shorter stays in hospital.

Maintenance therapy

The QUAZAR study, a phase III, randomized, double-blinded, placebo-controlled trial, evaluated CC-486, an oral, well-tolerated hypomethylating agent, as maintenance therapy in elderly patients above the age of 55 years with intermediate or high-risk AML after achieving first CR or CRi after intensive induction therapy who were ineligible for allo-HCT. The maintenance therapy was intended to be continued until death, relapse, or intolerable toxicity. According to a previous study, at a median follow-up of 41.2 months, CC-486 led to a significant improvement of OS compared to that in the placebo arm (24.7 months *vs*. 14.8 months, respectively; HR=0.69, 95% CI: 0.55-0.86; *P*=0.0009). The most frequently reported adverse events were grade 1 or 2 nausea, vomiting, and diarrhea; the most common grade 3 or 4 adverse events were neutropenia, anemia, and thrombocytopenia. Based on these results, the FDA and EMA granted approval of CC-486 for patients in CR/CRi unfit for allo-HCT or intensive consolidation therapy after intensive induction therapy.[78] In an accompanying study, presented at the 63rd American Society of Hematology annual meeting, in comparison to placebo, CC-486 prolonged OS and relapse-free survival in patients with mutated *NPM1*, with improvements beyond the prognostic benefit conferred by MRD negativity, suggesting that patients with mutated *NPM1* and MRD negativity can attain substantial OS benefit with CC-486 maintenance.[79] However, based on the shape of the Kaplan-Meier curves the effect seemed to be limited in time, as relapses appeared to be delayed rather than prevented. A recent retrospective analysis also showed that CC-486 prolonged the survival of patients with AML in remission independently of MRD status.[80]

Other oral medications are being evaluated as possible maintenance therapies, such as venetoclax in addition to azacitidine,[81] quizartinib and gilteritinib in *FLT3*-mutated AML and ivosidenib as well as enasidenib in *IDH1/2*-mutated AML.

Old and frail patients

Older patients are more likely to have comorbidities, impaired performance status, and poorer cytogenetic risk.[5] These factors contribute to poorer prognoses and poorer tolerance to intensive therapeutic regimens. Less intensive treatment options such as azacitidine and decitabine have become the backbone for the majority of combination therapy regimens for elderly patients.[36,37,74] Luckily, recent studies have changed the prospective of these patients making the achievement of long-lasting CR possible. The results of the VIALE-A trial revolutionized therapy in elderly patients. In this study 431 elderly unfit patients with AML, ineligible for standard induction therapy, were treated with azacitidine plus either venetoclax (aza-ven) or placebo. The median OS was longer in the aza-ven group than in the placebo group (14.7 *vs*. 9.6 months, respectively; HR=0.66, 95% CI: 0.52 to 0.85; *P*<0.001). A composite CR was achieved in 66.4% (95% CI: 60.6-71.9) of the patients in the aza-ven group and 28.3% (95% CI: 21.1-36.3) of the patients in the placebo group (*P*<0.001).[19] Since then, multiple studies have explored different backbone combination partners for venetoclax in older and younger patients. As a consequence, substances such as glasdegib[82] have been eclipsed by venetoclax in combination with hypomethylating agents. Recent studies have shown improvements in remission rates even in patients with *TP53* mutations, although this did not translate into longer OS. Further improvements in these difficult-to-treat patients were identified in a phase I/II study evaluating the combination of aza-ven and magrolimab, an anti-CD47 antibody that blocks the "don't eat me signal" on macrophages. Overall, high CR/CRi rates were reported; in particular in old and frail patients with *TP53*-mutated AML the CR/CRi rate was 100% (7/7) and MRD negativity, assessed by multicolor flow cytometry, was achieved by 57% (4/7).[83] Another study presented at the 63rd American Society of Hematology annual meeting was a phase II study evaluating venetoclax added to cladribine and low-dose cytarabine alternating with azacitidine in older and unfit patients with newly diagnosed AML.[84] Again, the CR/CRi rate among 60 evaluable patients was high (93%) and MRD-negativity was achieved by 43 of 51 evaluable patients (84%). Based on these studies, it is safe to say that venetoclax as an adjunct to different backbone therapies provides meaningful improvements in remission rates and, based on partial responses from these last studies, a clinically relevant improvement in OS compared to chemotherapy alone.

There are also preliminary results from studies of the combination of FLT3 or IDH inhibitors with azacitidine in older patients not fit for intensive chemotherapy. A phase II trial evaluated the efficacy of gilteritinib and azacitidine *vs*. azacitidine alone in 123 patients with newly diagnosed *FLT3*-mutated AML randomized 2:1. The composite CR rates were significantly higher for gilteritinib and azacitidine than for azacitidine alone (58.1 *vs*. 26.5%; *P*<0.001), however, the median OS was not different, being 9.82 months for the combination and 8.87 months for azacitidine alone (HR=0.916, 95% CI: 0.529-1.585; *P*=0.753).

IDH inhibitors

The AGILE trial evaluated ivosidenib as an adjunct to azacitidine in elderly patients with *IDH1*-mutated AML not fit for intensive therapy. One hundred and forty-six patients were randomized: 72 to ivosidenib plus azacitidine (median age, 76 years) and 74 to placebo and azacitidine (median age, 75.5 years). At a median follow-up of 12.4 months, event-free survival, defined as treatment failure, relapse from remission, or death, was significantly longer in the ivosidenib plus azacitidine group than in the placebo + azacitidine group (HR=0.33, 95% CI: 0.16-0.69; *P*=0.002). The median OS was 24.0 months in the group treated with ivosidenib plus azacitidine and 7.9 months in the group treated with placebo plus azacitidine (HR=0.44; 95% CI: 0.27-0.73; *P*=0.001). The composite CR rate with ivosidenib plus azacitidine was 53% (95% CI: 41-65) compared to 18% (95% CI: 10-28) with placebo plus azacitidine (*P*<0.0001). The frequency of all-grade differentiation syndrome, assessed by investigators, was 14.1% with ivosidenib plus azacitidine and 8.2% with placebo plus azacitidine[63] (NCT03173248).

Conclusions

Since 1973, induction therapy with cytarabine in combination with an anthracycline has been the standard of care for fit patients with AML.[85] In recent years, comprehensive genomic profiling for the most frequent AML mutations has become part of the clinical routine for most patients in economically developed countries. This new knowledge has culminated in the identification of several substances targeting crucial intracellular signaling pathways necessary for the growth of various forms of AML. However, used as single agents, these substances display moderate antileukemic activity. In contrast, when they are administered in combination with hypomethylating drugs or intensive chemotherapy, there is a meaningful improvement in their clinical activity.

The approval of the BCL-2-targeted therapy venetoclax has paved the way for exciting future research opportunities for patients deemed unfit to receive intensive chemotherapy, a population with previously very limited therapeutic options. Recently, improvements have been seen even in patients with adverse-risk AML harboring *TP53* alterations when treated with antibodies and venetoclax. The un-

answered question is whether older patients are the only ones who should be treated with non-intensive regimens. Consistent lack of superiority for intensive chemotherapy compared to aza-ven has been seen in several risk groups of elderly and younger patients with AML, mainly in retrospective analyses. This has led to the idea of offering non-intensive therapy regimens to younger patients as well. Indeed, this approach is being tested in different clinical trials. In the era of the COVID-19 pandemic, approaches that facilitate outpatient therapies are all the more preferable. Surrogate endpoints such as MRD may accelerate accurate clinical validation of new therapies. These new and exciting therapies, as well as the fact that we can detect sooner which patients will respond adequately to therapy, make the future of AML therapy brighter than ever.

Disclosures

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Contributions

SJ and RFS conceived, designed and wrote this review and gave final approval of the manuscript.

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