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LEUKEMIA (A AGUAYO, SECTION EDITOR)

New Treatment Options for Acute Myeloid Leukemia in 2019

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Abstract

Purpose of Review The extensive genomic characterization of acute myeloid leukemia (AML) led to the identification of a vast number of potential therapeutic targets. We review relevant data that have led to recent approval of new targeted therapies in AML and discuss the most promising drugs currently in development in this disease.

Recent Findings New formulations of cytotoxic agents, namely CPX-351 and gemtuzumab ozogamicin, improve the outcome of defined subgroup of patients. Midostaurin added to intensive chemotherapy is approved in *FLT3*-mutated AML. More selective *FLT3* inhibitors and the *IDH* inhibitors enasidenib and ivosidenib have shown significant single agent activity in the relapsed setting, and preliminary results of combination strategies are encouraging. The addition of the BCL2 inhibitor venetoclax appears to markedly improve the results of hypomethylating agents.

Summary The therapeutic armamentarium of AML now includes novel cytotoxic drugs, drugs targeting recurrent oncogenes, or functional vulnerabilities of leukemic cells. Further work is required to optimize their integration to the current framework of AML management, including allogeneic stem cell transplantation.

Keywords Acute myeloid leukemia · Targeted therapy · FLT3 inhibitors · BCL2 inhibitors · IDH inhibitors · Hypomethylating agents

Introduction

Acute myeloid leukemias (AML) are a heterogeneous group of diseases from the clinical, morphological and molecular standpoints, as outlined by the recent 2016 World Health Organization classification [1]. Several AML subgroups defined by recurrent cytogenetic and molecular abnormalities have markedly different outcomes with available therapies. The efforts to characterize AML genomics have shed light on its complex mutational landscape [2–4]. However, aside from acute promyelocytic leukemias, the prognosis of AML remains unsatisfactory, with less than 50% of younger patients and 20% of elderly (i.e., > 60 years) ones being cured with current treatments. For decades, the standard of care for fit patients has been a 7 + 3 intensive chemotherapy (IC) induction regimen, combining cytarabine and an anthracycline, followed by post-remission consolidation therapy often based on high dose cytarabine (HDAC) with or without allogeneic hematopoietic stem cell transplantation (alloHSCT) or less frequently in recent years, autologous HSCT [5]. The treatment of elderly AML patients deemed unfit for such intensive therapy on the base of poor performance status or comorbidities, remains notoriously difficult. Options range from best supportive care (BSC) only to low dose cytarabine (LDAC) or hypomethylating agents (HMA) [6]. The latter is increasingly considered instead of IC also for elderly patients with high-risk disease, such as secondary AML or unfavorable oncogenetics [7].

Following a long period of empirical testing of novel chemotherapy agents with limited success, the genomic characterization of AML, and translational research in relevant in vitro and in vivo pre-clinical models, has led to the identification of novel therapeutic targets. These include surface antigens, driver oncogenes, and cellular pathways. The

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progresses of medicinal chemistry are now turning these targets into clinical advances for AML patients. Once portrayed as a 'boulevard of broken dreams' the field of clinical research in AML is rapidly changing, with the approval by the Food and Drug Administration (FDA) of five drugs in the last 2 years, namely gemtuzumab ozogamycin, CPX-351, midostaurin, enasidenib, and ivosidenib. Here, we review the recent advances that led to the approval of these drugs along with some of the most promising treatments hopefully available in the next future.

Innovative Cytotoxic Treatments

Efforts have been made to improve the results of standard IC by addition of new cytotoxic agents, liposomal encapsulation, or more specific delivery through immunoconjugates [8].

Purine Analogs The addition of fludarabine or cladribine to HDAC-based or standard induction regimens is feasible and could be associated to superior anti-leukemic activity compared to 7 + 3 alone [9–12]. A clear survival advantage has yet to be proven and these regimens are not recommended by current ELN guidelines [13]. Clofarabine showed promising activity in the relapse setting, but it failed to improve survival when compared to standard IC or to LDAC in several randomized trials [14–17]. Although the combination of clofarabine and daunorubicin was inferior to FLAG-IDA as a consolidation treatment for adverse risk younger patients in the MRC AML17 trial, post-remission clofarabine combined with intermediate doses of cytarabine was associated with a significant reduction in relapse risk compared to standard HDAC in intermediate and high-risk patients not transplanted in first complete remission in the Acute Leukemia French Association (ALFA) 0702 study [18, 19].

CPX-351 is an innovative formulation fixing a synergistic 5:1 M ratio of cytarabine to daunorubicin within a liposomal carrier, allowing sustained drug exposure and intracellular delivery [20]. In a recently published phase III trial, CPX-351 was compared to 7 + 3 IC in elderly fit patients with secondary, therapy-related or de novo AML with myelodysplastic syndrome (MDS)-related abnormalities. In this unfavorable patients population, more than 40% of whom had been previously exposed to HMA, CPX-351 significantly improved the rate of composite complete remission (cCR, 48 vs. 33%) and overall survival (OS, median 9.6 vs. 6 months), with a comparable early death rate. Toxicities were similar, except for a longer time to neutrophil and platelet recovery in the CPX-351 arm. Fifty-two and 39 patients underwent alloHSCT in the CPX-351 and the 3 + 7 arm, respectively, and an exploratory landmark survival analysis from the time of alloHSCT markedly favored CPX-351, suggesting that not only the rate, but also the quality of responses was improved by this liposomal combination. Post-hoc sub-group analyses suggested that CPX-351 was less beneficial to patients with complex karyotype and with mutated FLT3, but future studies will be required to delineate more precisely which AML subsets from the heterogeneous set of 'high-risk' diseases included in this trial benefit most from CPX-351 [21•].

Gemtuzumab Ozogamicin The humanized anti-CD33 gemtuzumab ozogamicin (GO) immunoconjugate delivers the linked cytotoxic drug calicheamicin to CD33-expressing leukemic cells, after internalization and intracellular release. After being withdrawn from the market in 2010 following the unsuccessful phase III SWOG S0106 study which relied on a single 6 mg/m^2 dose at day 4 [22], different schedules of the drugs have been explored to reduce toxicity and maximize efficacy [23, 24]. Indeed, even lower doses (3 mg/m^2) induced meaningful responses and high saturation of the CD33 sites in initial studies. Besides, the rapid re-expression of CD33 molecules on cell surface after a first exposure to the drug suggested that the administration of fractionated doses could be beneficial [25]. Furthermore, the AML 17 trial confirmed that single doses higher than 3 mg/m^2 should not be employed because of increased incidence of veno-occlusive disease and early mortality [26]. A fractionated regimen of 3 doses of GO 3 mg/m^2 on days 1, 4 and 7, developed by the ALFA group showed to be effective in both the relapsed and frontline setting [25, 27]. In the ALFA-0701 phase III study, patients aged 50–70 with de novo AML were randomized to receive standard induction and consolidation with or without GO. cCR rate did not differ between the arms but GO was associated with a significantly longer event-free survival (EFS, median 17.3 vs. 9.5 months) and relapse-free survival (RFS). However, a higher incidence of grade ≥ 3 hemorrhages (22.9 vs. 9.5%) and a longer time to platelet recovery were observed with GO, but the incidence of veno-occlusive disease (4.6% of patients) was acceptable [28•]. Finally, an updated individual patient data-based meta-analysis including 3325 adult patients confirmed that addition of GO to IC in treatment-naive AML patients provided an OS benefit due to a reduced relapse risk. The absolute survival advantage was especially evident in patients with favorable cytogenetics and to a lesser extent in those with intermediate-risk cytogenetics, but not in those with high-risk disease [29].

Other Agents Vosaroxin, a quinolone-derived topoisomerase II inhibitor, showed single-agent activity in relapsed/refractory (R/R) AML and provided encouraging overall response rates (ORR) in combination with decitabine (DAC) [30, 31]. Unfortunately, the addition of vosaroxin to cytarabine, though improving the CR rate, failed to improve OS compared to cytarabine (1 g/m^2, d1-5) alone in the randomized phase III VALOR trial involving R/R AML patients [32]. Ongoing trials are exploring vosaroxin in combination with IC or HMA in untreated AML (NCT02658487 and NCT03338348).

Targeted Agents

The characterization of the mutational landscape of AML has led to the development of small molecules targeting recurrent driver mutations. These can represent alternative non-intensive strategies for patients who unfit for conventional therapies, but more importantly can be combined with IC or HMA to improve their activity.

FLT3 Inhibitors

The class III receptor tyrosine kinase (RTK) FMS-like tyrosine kinase 3 (*FLT3*) plays a key role in myelopoiesis. *FLT3* mutations occur in more than 30% of AML patients, often as secondary events, and lead to ligand-independent activation of the receptor promoting proliferation, survival, and resistance to apoptosis of (pre-)leukemic cells. The majority (~75%) of *FLT3* alterations are internal tandem duplications (ITD) associated with unfavorable prognosis when the mutant/wild-type (WT) allele ratio is high. Non-ITD *FLT3* alterations mostly involve point mutations in the tyrosine kinase domain (TKD). Targeting mutant FLT3 has been investigated with a number of type I (binding the gatekeeper domain) or type II (binding the activation loop) tyrosine kinase inhibitors with variable pharmacokinetics, selectivity for *FLT3* and potency in inhibiting FLT3-ITD and FLT3-TKD in vitro [33, 34].

Midostaurin The benefit of the addition of the multi-target tyrosine kinase inhibitor midostaurin to a standard 7 + 3 induction and HDAC consolidation program in *FLT3*-mutated AML patients younger than 60 was addressed in the phase III RATIFY trial. This study was a logistic *tour de force*, with 3279 patients screened and 717 randomized over 3 years in 17 countries, stressing the need for international collaboration to successfully conduct pivotal trials in molecularly-defined AML subsets. Addition of midostaurin 50 mg bid on days 8–21 of 7 + 3 and of 4 HDAC consolidation courses was well tolerated and no significant treatment-related adverse events (TRAE) grade ≥ 3 were noted, except for an increased incidence of rash. Midostaurin significantly prolonged OS compared to placebo (median 74.7 vs. 25.6 months) and, albeit the absolute benefit was modest (4 years OS rate 51 vs. 44%), it was apparent for both TKD and ITD mutations. Midostaurin was not associated with a significant improvement of CR rate but there was a trend towards more frequent alloHSCT in first CR in the midostaurin arm. Furthermore, the survival after transplant of patients receiving alloHSCT in first CR was superior in the midostaurin arm [35•]. Though no MRD assessment was performed, these results suggest that the survival advantage provided by midostaurin resulted from an improved quality of responses and prevention of early relapses. In 174 patients not transplanted in first CR, no benefit of maintenance with midostaurin was apparent, perhaps because of limited patient numbers [36].

Sorafenib The type II multi-kinase inhibitor sorafenib was tested in association with IC in younger untreated AML patients in the randomized SORAML trial, which reported a significant EFS benefit over placebo in both *FLT3*-mutated and WT cases. This did not translate into significantly prolonged OS, because of the lower rate of second remission in post-sorafenib relapsed AML [37]. In association with AZA, sorafenib demonstrated significant activity in both relapsed (cCR 40–50%) and newly diagnosed (cCR 70%) FLT3-ITD AML, but the number of patients treated was small [38–40]. Besides, encouraging results were obtained in non-randomized studies evaluating this drug as a maintenance treatment post alloHSCT, with more than 90% RFS 1 year after transplant [41–43].

Quizartinib is a more selective and potent inhibitor of FLT3-wildtype (WT) and FLT3-ITD without activity on FLT3-TKD. Quizartinib was used as single agent in a large phase II trial involving 333 R/R AML patients. In the FLT3-ITD positive population ($n = 248$), the cCR rate was 50%. However, CRs were rarely seen (3%) since most patients remained cytopenic, possibly because of the significant inhibition of cKIT exerted by this drug. Though median duration of response was less than 3 months, 35% of younger patients could receive an alloHSCT. Interestingly a significant proportion of patients with FLT3-WT also responded, with a cCR rate > 30% in this population. Significant non-hematological grade ≥ 3 TRAE were limited to QTc prolongation (10%) and reversible gastrointestinal symptoms [44]. Preliminary results of the randomized phase III QuANTUM-R study, which randomized 367 R/R FLT3-ITD positive AML patients to quizartinib versus salvage chemotherapy (mostly, but not exclusively intensive regimens), showed a significant, albeit limited, improvement of OS (median 6.3 vs. 4.8 months) [45]. This limited survival benefit is likely due to the selection or adaptation of both cell-intrinsic and stroma-mediated resistance to FLT3 inhibition. This has been best studied in FLT3-ITD patients, where it notably arises from activation of other RTKs such as AXL, or acquisition of point mutations in the gatekeeper domain (F691) or the activation loop (D835) of FLT3. The latter is notably frequent after quizartinib exposure [46].

Gilteritinib is a highly potent inhibitor of FLT3-ITD and, albeit to a lesser extent, FLT3-TKD that also targets AXL. In a large phase I/II study involving 252 R/R AML patients gilteritinib demonstrated an encouraging 30% cCR rate on the whole population, reaching 41% among the 169 FLT3 mutant patients who received a dose ≥ 80 mg/day, with a CR rate of 11%. The subgroup of patients harboring both ITD and TKD mutations responded as well, whereas only 1 of the 16 TKD only-mutated cases achieved CR. Significant QTc prolongation was rarely

seen with gilteritinib, and most common extra hematological grade ≥ 3 TRAE were diarrhea and hepatic enzyme elevation [47]. Similar results were confirmed in a small phase I study [48]. Interestingly, around 25% of cCR patients achieved MRD negativity, which was associated with a superior OS [49].

Preliminary results of another inhibitor active on both FLT3-ITD and TKD, crenolanib, in *FLT3*-mutated AML revealed encouraging cCR rates, comparable with the results obtained by the other two selective inhibitors [50]. Phase II/III clinical trials evaluating these inhibitors in the relapse setting (alone or in combination), as first-line therapy in combination with IC or HMA or as a maintenance, are ongoing and compassionate use programs are active in many countries.

IDH Inhibitors

The isocitrate dehydrogenases IDH1 and IDH2 catalyze the conversion of isocitrate to α-ketoglutarate (αKG) in the cytoplasm and mitochondria, respectively. Hotspot mutations in *IDH1* and *IDH2* are found in about 20% of AML patients and encode a neomorphic enzyme that both hampers the normal enzymatic activity and confers the ability to catalyze the conversion of αKG to the oncometabolite R-2-hydroxyglutarate (2-HG) which impedes the function of all αKG-dependent oxygenases involved in DNA (TET2) or histone demethylation, thus leading to altered gene expression. Inhibitors of the neomorphic mutant IDH enzymes are able to markedly decrease total serum 2-HG, reduce abnormal histone hypermethylation and finally restore myeloid differentiation [51].

Enasidenib a potent and selective inhibitor of mutant IDH2, was tested in a phase I/II trial, which evaluated 239 patients with mutant *IDH2* and advanced myeloid malignancies, mostly R/R AML. Enasidenib was well tolerated, with leukocytosis, hyperbiluribinemia, and differentiation syndrome as the most significant TRAE; severe hematologic toxicities were rare. Among patients with R/R AML, ORR was 40% and cCR and CR rates were 26% and 19%, respectively, with a median duration of CR of 8.8 months. Median time to first response was 1.9 months but more than 3 months were required to achieve CR. With a median follow-up of 7.7 months, median OS was 9.3 months. While CR patients had the longest survival (median OS 19.7 months), achievement of responses less than CR nonetheless provided a clear survival benefit [52•]. Enasidenib is mostly a differentiation therapy [53]. Several mechanisms of resistance have already been proposed, including selection of *IDH1*-mutated subclones, and point mutations in *IDH2* [54, 55].

Ivosidenib a selective inhibitor of mutant IDH1, was explored in a phase I dose escalation and dose-expansion study including 258 patients with *IDH1*-mutated hematologic malignancies. Among the 125 R/R AML patients of the primary efficacy population, ORR, cCR, and CR rate were 41%, 30%, and 22%, respectively. Median time to cCR was 2.7 months and median cCR duration was 8.2 months. After a median follow-up of 14.8 months, median OS was 8.8 months and for cCR patients 18-month OS was 50%. Ivosidenib was well tolerated with leukocytosis, QTc prolongation and differentiation syndrome being the most relevant TRAEs [56•].

Both drugs have been approved by the FDA for the treatment of R/R AML as single agents, and compassionate use programs are active in some countries. A preliminary report on the combination of enasidenib or ivosidenib and AZA showed an encouraging ORR of 70% in unfit untreated *IDH1/2*-mutated AML patients [57] and several phase II and III clinical trials are evaluating IDH inhibitors in association with IC and HMA. Besides, new agents targeting mutant IDH enzymes, including the dual IDH1/IDH2 inhibitor AG-881 (NCT02492737), are being tested in early clinical studies.

Mutant p53 Activating Agents

TP53 mutations are found in 5–10% of de novo AML patients and up to 30% of patients with therapy-related disease, and the outcome of *TP53*-mutated AML remains very unfavorable. Most *TP53* mutations result in a missfolded transcription factor not able to bind DNA. APR-246 is a first-in-class p53 activating agent that restores the normal folding of mutant p53 by binding key cysteine residues [58]. Preliminary but exciting results of a phase Ib/II combination study combining APR-246 with AZA in *TP53*-mutated MDS and AML have been presented, with 9 of the 9 evaluable patients responding (8/9 in CR) [59].

Targeting Key Cellular Pathways

Besides genomics, functional studies in pre-clinical models have uncovered the dependency of AML cells on several intracellular pathways. A vast number of drugs targeting these pathways are currently in development, among which those altering apoptosis regulation are the most promising so far. Those that have entered clinical trials are summarized in Table 1. Whether oncogenetic biomarkers will be available for these drugs, or whether alternative 'functional' biomarkers will be required remains an open question [69].

Targeting Apoptosis Many AMLs are highly dependent on the anti-apoptotic protein BCL-2, which sequesters pro-apoptotic proteins, allowing evasion of AML cells from apoptosis. Venetoclax (formerly ABT-199) is a BCL-2 specific inhibitor that does not carry the limiting hematological toxicity caused by combined BCL-XL inhibition seen with previous generations of pro-apoptotic drugs such as ABT-737 [70]. After

Table 1 Selected cellular targets (excluding immunotherapy) currently tested in adult AML clinical trials

Target	Agent	Association	Phase of developement	AML population	Reference
Smoothened	Glasdegib /vismodegib	3 + 7, HMA or LDAC/ ribavirin, DAC	III/I	Untreated and R/R	NCT03416179, [60]/ NCT02073838
MDM2	Idasanutlin/ milademetan/ AMG-232	IDAC, venetoclax/ alone, AZA, DAC	III/I/I	Untreated and R/R	NCT02545283, NCT02670044, [61]/ NCT03671564,NCT02319369/ NCT03041688
MDM2 and MDMX	ALRN-6924	Alone	I	R/R	NCT02909972
E-selectin	Uproleselan	IC	III	R/R	NCT03616470, [62]
Exportin 1	Selinexor	IC	II	Untreated and R/R	NCT02835222, NCT02416908, NCT03071276, [63]
CXCR4	LY2510924	IC	I	R/R	NCT02652871
CXCL12	CX-01	IC	I-II	Untreated	NCT02873338, [64]
MCL1	AMG-176/ S64315/ AMG-176	Alone	I/I/I	R/R	NCT02675452, NCT02979366, NCT03465540
AXL	BGB324	LDAC or DAC	Ib/II	Untreated and R/R	NCT02488408
CDK9	Alvocidib/azd4573	IC or venetoclax/alone	I-II/I	Untreated and R/R	NCT03563560, NCT03441555, NCT03298984, NCT02520011/ NCT03263637
CDK4,6	Palbociclib	Single agent or combinations	Ib-II	MLL-r, R/R and untreated	NCT02310243, NCT03132454, [65]
CDK1, 2,5, 9	Dinaciclib	Venetocax	I	R/R	NCT03484520
VEGFR3, FGFR, PDGFR	Nintedanib	IC or HMA	I-II	R/R	NCT02665143, NCT03513484
VEGFR (and others RTK)	Regorafenib	Alone	I	R/R	NCT03042689
CSF-1R, KIT, and FLT3	Pexidartinib	Alone	I-II	R/R	NCT02390752
MET (and others RTK)	Merestinib	LY2874455	I	R/R	NCT03125239
FGFR	LY2874455	Merestinib	I	R/R	NCT03125239
MEK	Cobimetinib	Venetoclax	I	R/R	NCT02670044
Akt/ERK	ONC201	Alone or LDAC	I-II	R/R	NCT02392572
SYK	Entospletinib/ TAK-659	IC/alone	Ib/II	Untreated and R/R	NCT02343939, [66]/ NCT02323113
Grb2	BP1001	LDAC	II	Untreated	NCT02781883
Wnt/β-catenin	CWP232291	IDAC	I-II	R/R	NCT03055286
STAT	OPB-111077	Alone	Ib	R/R	NCT03197714
PARP	Talazoparib	DAC	I-II	Untreated and R/R	NCT02878785
PLK-4	CFI-400945	Alone	I	R/R	NCT03187288
PLK-1	Onvansertib	LDAC or DAC	I-II	Untreated and R/R	NCT03303339
Aurora kinase B	AZD2811	Single agent	I-II	Untreated and R/R	NCT03217838
RARα (agonist)	IRX5183/SY-1425	Single agent or combinations	I/II	R/R	NCT02749708/ NCT02807558
TRAIL receptor (agonist)	ABBV-621	Alone or venetoclax	I	R/R	NCT03082209
MUC-1	GO-203-2C	Alone or with decitbine	I-II	R/R	NCT02204085

Table 1 (continued)

Target	Agent	Association	Phase of developement	AML population	Reference
PIM/FLT3	SEL24	Alone	I-II	Untreated and R/R	NCT03008187
PIM-1, 2, 3	LGH447/INCB053914	Alone or with midostaurin	I	R/R	NCT02078609/ NCT02587598, [67]
Proteasome	Ixazomib	IC	I	Untreated	NCT02582359
SF3b complex	H3B-8800	Alone	I	Untreated and R/R	NCT02841540
MELK	OTS167	Alone	I-II	R/R	NCT02882322
CRBN	CC-90009	Alone	I	R/R	NCT02848001
EphrinB4	EphB4-HSA	IC	I	R/R	NCT03519984
MYC	APTO-253	Alone	Ib	R/R	NCT02267863
Respiratory complex I	IACS-010759	Alone	I	R/R	NCT02882321
Dihydroorotate DH	ASLAN003/ BAY2402234	Alone	IIa/I	Untreated and R/R	NCT03404726
Inosine monophosphate DH	FF-10501-01	Alone	I-II	R/R	NCT02193958, [68]

AZA azacytidine, *DAC* decitabine, *DH* dehydrogenase, *HMA* hypomethylating agents, *IC* intensive chemotherapy, *IDAC* intermediate dose ARA-C, *LDAC* low dose ARA-C, *MLL-r* MLL-rearranged, *R/R* relapsed or refractory

demonstrating modest single agent activity in R/R AML (cCR 16%) in a phase I study [71], venetoclax was tested in combination with LDAC in 71 newly diagnosed elderly AML patients, showing a cCR rate of 62% and a median duration of cCR of 14.9 months; median OS of the whole cohort was 11.4 months [72]. When combined with HMA, venetoclax was associated with cCR rate of 61% and a good tolerability in newly diagnosed AML patients, the main TRAEs being neutropenia and nausea [73]. The updated results of the latter trial including 145 patients, with a median follow-up of 15.1 months, confirmed the high remission rate (cCR 67%) with a median duration of response of 11.3 months, and a median OS of 17.5 months [74•]. In the relapsed setting, the association of HMA and venetoclax showed significant activity, with ORR of 26 to 76% in small retrospective series, which included also cases with previous HMA exposure [75, 76]. It has been suggested that *IDH1/2*-mutated and *NPM1*-mutated AML have a high response rate to venetoclax, but this warrants confirmation in larger series [71].

Phase II/III trials evaluating venetoclax in association with HMA, LDAC, IC, or other targeted agents are ongoing and drugs targeting MCL1, another pro-survival protein which has been implicated in venetoclax resistance [77], are in development and tested in phase I/II studies (Table 1).

Targeting Epigenetics

Epigenetic alterations are extremely frequent in AML, as a result of somatic mutations in epigenetic regulators involved in the control of DNA methylation (*DNMT3A*, *IDH1/2*, *TET2*) or covalent histone marks (*ASXL1*, *EZH2*), fusion proteins of epigenetic regulators (e.g., *MLL*/*KMT2A* fusions) or because of 'epimutations' accumulated during aging of hematopoietic stem cells [78]. Proof of principle of targeting epigenetic alterations in AML stems from the FDA-approved HMAs AZA and DAC, which act as DNA methyltransferase inhibitors. Results of these first-generation HMAs remain unsatisfactory and several efforts have been made to improve them.

Modified Schedules Conflicting results have been reported over the prolonged 10 days schedule of DAC and, while some studies showed encouraging CR rates around 40%, including a striking 100% in *TP53*-mutated AML, other experiences did not confirm its superiority over a standard 5-day regimen [79–81]. An EORTC-GIMEMA trial is currently comparing the 10-day DAC schedule vs. 7 + 3 in elderly fit patients (NCT02172872).

Maintenance Treatment HMA have been explored in the maintenance setting: a recent report from the HOVON group showed a significant 12 months DFS benefit (63 vs. 30%) of low dose AZA (50 mg/m^2/day for 5 days per cycle) vs. observation in 117 elderly AML patients in cCR after IC [82],

contrasting with previous negative reports [83]. DAC combined with panobinostat and DLI is being tested as maintenance after alloHSCT in poor risk patients [84]. An oral formulation of AZA, CC-486, demonstrated some activity in both de novo and R/R AML patients [85] and it is being studied as a maintenance treatment (NCT01757535), due to its convenient route of administration and the extended dosing schedule, which might improve efficacy.

New HMAs Guadecitabine is a dinucleotide of decitabine and deoxyguanosine which was designed to resist degradation by cytidine deaminase, thus prolonging half-life. Guadecitabine demonstrated significant activity in both naive (cCR rate > 50%) and R/R AML patients (cCR rate 23%) [86, 87]. It was recently announced that the randomized phase III study of guadecitabine versus physician choice in treatment-naive unfit patients (ASTRAL-1, NCT02348489) did not meet its co-primary endpoints of superior CR rate and OS [88]. Further report on this study is thus awaited. Phase III randomized studies in R/R AML and a phase II trial combining guadecitabine with DLI in the post alloHSCT setting are ongoing. ASTX727, an oral combination of DAC with a cytidine deaminase inhibitor, is being tested in a phase III trial compared to DAC in MDS and low blast count AML (NCT03306264).

Combining HMA Aside from the aforementioned trials with BCL2, IDH, and FLT3 inhibitors, many combinations of HMA with new drugs, mostly selected on an empirical basis, have been performed and have been extensively reviewed elsewhere [89]. Notably, combinations with various histone deacetylase (HDAC) inhibitors reported disappointing results. The most recent one, a phase II trial combining AZA with pracinostat in older unfit AML patients ($n = 50$) showed an encouraging cCR rate of 52% and a median OS of 19.1 months [90] that warrants confirmation in an ongoing phase III randomized trial (NCT03151408). A phase 1b study combining azacitidine and pevonedistat, an inhibitor of the NEDD8-activating enzyme (implicated in the ubiquitin ligase-proteasome mediated degradation of several substrates), reported a cCR of 39% and a median duration of response of 8.3 months in 64 elderly newly diagnosed AML patients. The treatment was well tolerated and the dose limiting toxicity was liver enzyme elevation [91]. A phase III randomized trial in MDS and low blast count AML evaluating this association vs. single agent AZA (NCT03268954), along with other combination studies, are ongoing.

New Families of Epigenetic Drugs Progresses in the understanding of the chromatin machinery governing gene expression and improvements in medicinal chemistry have led to the development of a number of new drug classes targeting enzymes involved in writing (EZH2, DOT1L, MLL), reading (BET bromodomains) or erasing (LSD1) histone marks involved in activating or repressing gene expression. These drugs classes have shown promising activities in various pre-clinical models of AML, but their clinical development is in an early stage.

BET (bromodomain and extraterminal) proteins bind acetylated-lysine residues on histones to alter transcription and govern the execution of the leukemic program driven by many oncogenes such as MLL (*KMT2A*) fusions. In a phase I study in R/R AML, the BET inhibitor OTX015 showed a modest but clinically significant activity in some patients [92]. Pinometostat, an inhibitor of the DOT1L (disrupter of telomeric silencing 1-like) histone methyltransferase, an enzyme also involved in orchestrating the leukemic programme of MLL fusions, was tested in a recently reported trial focusing mostly on MLL-rearranged R/R AML. Pinometostat showed some clinical activity as single agent, including 2 CRs, both in t(11;19) cases [93]. Pre-clinical studies are still warranted to identify the AML subgroups most likely to benefit from these novel agents and nominate optimal combinations, given the expected limited single-agent activity of these compounds in unselected AML.

Future and Perspectives

The increasing number of novel therapeutic options in AML is challenging the "one-size-fits-all" paradigm of upfront AML management. In future years, it is possible that the choice of IC regimen will depend on cytogenetic and molecular risk: patients with adverse cytogenetics and/or secondary and therapy-related AML could be treated with CPX-351, while some subgroups such as core binding factor AMLs could benefit from the addition of GO and/or KIT inhibitors like dasatinib [94].

Beyond the addition of midostaurin to IC in *FLT3*-mutated AML, novel FLT3 and IDH inhibitors could also be effectively combined with standard IC or HMA. In elderly patients not eligible for IC, the combination of HMA or LDAC with venetoclax, or, though data is less mature, pevonedistat, or pracinostat, could represent interesting options.

How oncogenetics and functional biomarkers will be integrated to deliver personalized-therapies in AML remains an open question. The revolution of precision medicine is also a challenge for clinical research. Innovative trial design, beyond the "pick a winner" approach [95] will be required to identify which drugs or combinations are beneficial to which AML subgroup. Drugs targeting epigenetic marks are particularly challenging from this standpoint, because they often lack a strong oncogenetic biomarker, may be active only in specific combinations, and may require prolonged exposure before obtaining a response. This drug profile is particularly disadvantaged in the current development plan of novel agents in AML focusing on small unselected patients' cohorts in an advanced phase of the disease, as single agent or combined with reference options such as HMA. The BEAT AML 'umbrella' trial is particularly interesting from that standpoint. Patients are enrolled into a single 'master' trial at

diagnosis, then assigned to appropriate arms based on an extensive centralized oncogenetic workup [96].

Finally, alloHSCT still represents one of the most effective treatment for AML. New immunotherapy approaches, albeit still in an earlier phase of development in AML compared to other hematological malignancies, are very promising and will likely play an important role in the future (recently reviewed elsewhere [97]). In this rapidly evolving context, predicting patients' prognosis and addressing the benefit of alloHSCT will be increasingly challenging, and the aid of knowledge banks of genomic and clinical data from large cohorts will be required, if constantly updated [98].

Conclusion

Drug development in AML is shifting from 'boulevard of broken dreams' to 'hope avenue.' However, the current surge of novel clinically active agents in AML is rather the 'end of the beginning' than the 'beginning of the end.' It represents a formidable challenge that will require dedication and collaboration between clinicians, translational hematologists, and industry to be translated into substantial benefit for our patients.

Compliance with Ethical Standards

Conflict of Interest Marco Cerrano declares that he has no conflict of interest.

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