New drugs before, during, and after hematopoietic stem cell transplantation for patients with acute myeloid leukemia

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Abstract

The treatment of acute myeloid leukemia (AML) has evolved over the past few years with the advent of next-generation sequencing. Targeted therapies alone or in combination with low-dose or high-intensity chemotherapy have improved the outcome of patients with AML treated in the frontline and relapsed/refractory settings. Despite these advances, allogeneic stem cell transplantation (allo-HCT) remains essential as consolidation therapy following frontline treatment in intermediate- and adverse-risk and relapsed/refractory disease. However, many patients relapse, with limited treatment options, hence the need for post-transplant strategies to mitigate relapse risk. Maintenance therapy following allo-HCT was developed for this specific purpose and can exploit either a direct anti-leukemia effect and/or enhance the *bona fide* graft-*versus*-leukemia effect without increasing the risk of graft-*versus*-host disease. In this paper, we summarize novel therapies for AML before, during, and after allo-HCT and review ongoing studies.

Introduction

The past decade marked a revolution in the treatment of acute myeloid leukemia (AML) with the advent of next-generation sequencing, leading to the discovery of new mutations and a better understanding of the biology of AML. Following these innovations, the landscape of AML therapy has evolved rapidly; since 2017, several novel therapies have received regulatory approval, including CPX-351,[1] midostaurin,[2] gilteritinib,[3] ivosidenib,[4] enasidenib,[5] venetoclax,[6,7] and glasdegib,[8] and gemtuzumab ozogamicin (GO) has re-emerged.[9] Following these approvals, numerous doublet and triplet combinations have been tested in which targeted therapy was added to intensive or low-intensity chemotherapy and/or to other targeted agents. In patients lacking targetable mutations, the standard of care remains intensive chemotherapy in fit patients or low-intensity treatment in unfit patients. Several groups of patients, particularly those carrying high-risk mutations, namely *TP53* mutations, and complex karyotype, still have a dismal prognosis. Minor changes in the treatment of this category of patients have occurred, with only few drugs being studied for *TP53*-mutated disease, including APR-246 (eprenetapopt) and anti-CD47 monoclonal antibodies.[10,11] Other novel drugs being tested in

MLL-rearranged and *NPM1*-mutated relapsed AML, are menin inhibitors, which led to an overall response rate of 44% in that population.[12] Following induction therapy, consolidation options include chemotherapy in favorable-risk disease or allogeneic hematopoietic cell transplant (allo-HCT) in intermediate- and adverse-risk AML. The optimal strategy depends on donor availability, patient- and disease-related characteristics, and the benefits of treatment weighed against treatment-related mortality. In this review, we summarize novel therapeutic approaches for AML before transplant. In addition, we discuss new combinations for conditioning regimens prior to allo-HCT, and we elaborate on post-allo-HCT maintenance strategies to diminish relapse.

Therapies available for use prior to allogeneic hematopoietic cell transplantation

Conventional treatment

Since the 1970s, the mainstay of first-line treatment in young, fit patients with AML has been the "7 + 3" regimen, serving as backbone therapy.[13]

This is usually followed by consolidation therapy to achieve lasting remission. This regimen consists of 7 days of continuous, standard-dose cytarabine (100-200 mg/m^2 daily), along with anthracycline during the first 3 days and is usually reserved for younger, fit patients. Higher doses of cytarabine have been associated with a small added survival benefit relative to the increased toxicities.[14,15] This benefit is more pronounced in young patients <46 years of age, as shown in the EORTC-GIMEMA AML12 trial. In this study, patients aged between 15-60 years were administered standard-dose cytarabine (100 mg/m^2 continuous infusion over 10 days) or high-dose cytarabine (3,000 mg/m^2 every 12 hours on days 1, 3, 5, and 7). Overall survival (OS) was significantly improved for patients receiving high-dose cytarabine compared to patients receiving standard-dose cytarabine (51.9% *vs.* 43.3%, respectively; *P*=0.009).[16] On the other hand, 60 or 90 mg/m^2 of daunorubicin and 12 mg/m^2 of idarubicin have yielded similar survival and complete remission (CR) rates.[14,17,18] The combination of fludarabine, cytarabine, granulocyte colony-stimulating factor (G-CSF), and idarubicin (FLAG-IDA), previously reserved for relapsed disease, is an alternative induction regimen yielding similar results, especially in favorable-risk disease.[19] Moreover, the use of FLAG has been demonstrated to provide superior relapse-free survival, compared to idarubicin and cytarabine (*P*=0.046), in treating core-binding factor-AML.[20] The UK MRC AML 15 trial showed a superior log-reduction reduction in minimal residual disease (MRD) with FLAG-IDA compared to the "7+3" regimen with or without etoposide, but this did not translate into a difference in OS.[21] These conventional regimens offer high rates of remission and prolong OS in patients aged <60 years with newly diagnosed AML, but not in older patients, since up to 70% of patients >65 years die within 1 year of diagnosis.[22]

Newer laboratory techniques, namely next-generation sequencing, identified mutations critical in the pathogenesis of AML leading to the development of targeted therapies. This novel arsenal of targeted drug therapies used as monotherapy or in combination with conventional treatments has revolutionized the treatment landscape of AML. GO is an anti-CD33 monoclonal antibody that was initially approved by the Food and Drug Administration (FDA) for the treatment of CD33-positive AML in first relapse in older patients before being withdrawn because of reports of increased mortality in the SWOG trial in the group treated with "7+3" and GO.[23] A meta-analysis of five trials involving more than 3,000 AML patients treated with GO in addition to standard therapy reported a reduction in relapse (*P*=0.0001) and improved survival (*P*=0.01) without increasing mortality in patients with favorable- and intermediate-risk cytogenetics.[24] Currently, GO is approved by the FDA and European Medicines Agency (EMA) for treating adult patients with newly diagnosed CD33-positive AML

at a dose of 3 mg/m^2 on days 1, 4, and 7 with the "7+3" regimen. The addition of GO to the FLAG regimen has also demonstrated superiority over the long-used FLAG-IDA regimen in core-binding factor AML, achieving higher remission rates.[25] A head-to-head comparison of "7+3"+GO and FLAG-IDA+GO regimens is needed in patients with core-binding factor AML.

In patients >65 years, treatment choices become more challenging given increased cytogenetic abnormalities and somatic mutations, and thus higher-risk disease, unpredictable response to chemotherapy, and increased chance of treatment-related mortality. Although prognosis is poor in this group compared to that in younger, fitter patients, induction chemotherapy remains standard, whenever possible, offering better outcomes than palliation.[26] In this patient population, hypomethylating agents (HMA), alone or in combination, have been shown to play a significant role, such that azacitidine or decitabine alone demonstrated superiority over low-dose cytarabine (LDAC) or supportive care in two cornerstone trials.[27,28] Novel therapies in AML prior to allo-HCT are described below. Trials for which results have been published are summarized in Table 1.

Novel therapies
CPX-351

CPX-351 is a novel liposomal carrier containing cytarabine and daunorubicin in a fixed 5:1 molar ratio. It was first studied in a phase I dose-escalation study in 2011, in which the maximum dose tolerated was 100 units/m^2, and adverse events were consistent with those of cytarabine and daunorubicin individually.[29] A phase II trial randomizing 126 older patients with untreated AML in a 2:1 fashion to receive CPX-351 or the "7+3" regimen documented higher response rates in the CPX-351 arm (66.7% *vs.* 51.2%; *P*=0.07).[1] A subgroup analysis of cases with secondary AML demonstrated notably improved response rates (57.6% *vs.* 31.6%, *P*=0.06), event-free survival (EFS) (hazard ratio [HR]=0.59; *P*=0.08), and OS (HR=0.46; *P*=0.01) with CPX-351.[1] This compound was later approved by the FDA for the treatment of newly-diagnosed, therapy-related AML, and AML with myelodysplastic syndrome (MDS)-related changes based on results of a phase III trial comparing CPX-351 with the "7+3" regimen in which OS was improved with the liposomal formulation (HR=0.69; *P*=0.005) with an improved CR rate of 38% compared to 26% (*P*=0.035).[30] More patients in the CPX-351 arm (56%) received allo-HCT than in the "7+3" arm (46%).[31] At a median follow-up of 60 months, the median OS was not reached in the CPX-351 arm while it was 10.3 months in the "7+3" arm (HR=0.51). This study showed the impact of induction therapy on transplant outcomes, offering older patients with AML high CR rates and prolonged survival after CPX-351 induction therapy followed by allo-HCT. An Italian group re-

ported similar results with CR rates of 70.4%.[32] Patients in this study who had undergone allo-HCT had improved outcomes, thus highlighting the potential impact of CPX-351 on post-HCT outcomes.[32] Its use was also investigated in the frontline setting to treat AML patients at high risk of mortality from standard induction in a phase II open-label trial.[33] Fifty-six patients were enrolled to receive 50, 75, or 100 units/m^2 on days 1, 3, and 5.[33] The composite CR was lowest in the 50 units/m^2 arm, although the difference was not statistically significant (19% *vs.* 38% *vs.* 44%; *P*=0.35).[33] The median OS was 4.3 months in the 50 units/m^2 arm compared to 8.6 and 6.2 months in the 75 and 100 units/m^2 arms, respectively, thus underscoring the efficacy, safety, and tolerability at the substandard dose of 75 units/m^2 in some patients at high risk of treatment-related mortality.[33] Currently, CPX-351 is being investigated in the relapsed/refractory (R/R) setting in combination with *FLT3* tyrosine kinase inhibitors (TKI), gilteritinib (NCT05024552) and quizartinib (NCT04128748), and GO, an anti-CD33 antibody drug conjugate (NCT03904251); in the frontline setting combined with fludarabine (NCT04425655), venetoclax (NCT04038437), quizartinib (NCT04128748) and palbociclib (NCT03844997); in therapy-related AML/MDS with glasdegib (NCT04231851); and in older patients with GO (NCT03878927).

BCL-2 inhibitors

B-cell lymphoma 2 (*BCL-2*) protects cells against apoptosis, and its expression in AML is associated with decreased sensitivity to cytotoxic therapy and, therefore, a higher probability of relapse. Venetoclax is an orally bioavailable inhibitor of *BCL-2*. Before its introduction for AML, it was FDA-approved for treating 17p-deletion-positive chronic lymphocytic leukemia. Early studies showed only modest efficacy of venetoclax monotherapy in treating R/R AML.[34] However, the promising results of two large phase Ib/II trials combining an HMA or LDAC with venetoclax led to the FDA approval of venetoclax combined with azacitidine, decitabine, or LDAC for older (>75 years) patients, unfit for intensive chemotherapy, with the HMA-venetoclax combination being the most commonly used.[35,36] The two phase III trials, VIALE-A and VIALE-C, demonstrated a significant survival benefit from combining venetoclax with a HMA.[6,7] The VIALE-A trial included patients >75 years, unfit for intensive chemotherapy *without* prior exposure to HMA.[6] Patients were randomized to receive either venetoclax-azacitidine or azacitidine alone: the CR rate was 36.7%, the clinical CR rate was 66.4%, and the median OS was 14.7 months in the group treated with the combination.[6] In contrast, 20% of patients in the VIALE-C trial had been previously exposed to HMA treatment. Patients in this trial were randomized to receive either venetoclax-LDAC or LDAC alone: the median OS improved from 4.1 to 7.2 months with the addition of venetoclax, with a 25% re-

duction of the risk of death.[7] These two trials established the combination of venetoclax-HMA as a standard of care for AML patients unfit for intensive therapy. It is essential to highlight that CR rates were significantly improved with this combination in all disease subgroups regardless of positive or negative prognostic mutations such as *NPM1*, *IDH-1/2*, or *FLT3*-ITD. This creates room for debate regarding patients with specific targetable mutations who responded to venetoclax-HMA. Do we combine novel drugs targeting mutations with venetoclax, HMA, or all three? The answer will depend on the safety profile of the triple drug combination and large randomized trials should be conducted to compare various doublet combinations to triplet combinations.

A recent prospective trial assessed the use of a venetoclax-azacitidine combination as a bridge to allo-HCT using historical patients who had received intensive chemotherapy prior to allo-HCT as the comparison group.[37] Patients who received venetoclax-azacitidine were older and had more secondary AML and adverse cytogenetics. They received mainly reduced intensity conditioning (RIC). The 12-month non-relapse mortality, relapse-free survival (RFS), and OS were 19.1%, 58%, and 63% in the venetoclax-azacitidine group compared to 11.8%, 54%, and 70% in the historical intensive chemotherapy group.[37] Another retrospective single-center study compared outcomes of patients >60 years of age who received induction venetoclax-azacitidine followed by allo-HCT to the same population of patients eligible for transplant but who chose to defer it.[38] The median OS was not reached for patients who underwent allo-HCT compared to 518 days for patients who did not (*P*=0.01), reinforcing the role of allo-HCT even in older patients. Those results are also valid for patients who receive triplet induction. In a phase II trial, *FLT3* inhibitors in combination with venetoclax and decitabine (for 10 days) were studied in patients with newly diagnosed and R/R *FLT3*-mutated AML ≥60 years old.[39] Four patients in the newly diagnosed cohort received consolidation with allo-HCT, followed by maintenance in two patients. At 2 years, all four patients were still alive. Hence, the use of triplet induction followed by allo-HCT followed by maintenance could improve long-term survival of newly diagnosed older patients with AML.[39] More data are needed to confirm these findings.

Venetoclax has since been studied in various combinations including with intensive chemotherapy. The MD Anderson Cancer Center group conducted a phase Ib/II trial of medically fit R/R or newly diagnosed AML patients treated with FLAG-IDA combined with up to 14 days of venetoclax. After an initial high rate of grades 3-4 febrile neutropenia in the first phase of the trial, chemotherapy doses were adjusted and the duration of venetoclax treatment reduced from 21 to 14 days, with a good safety profile. Results demonstrated robust efficacy, with 90% of

newly diagnosed AML patients achieving CR and 96% achieving MRD negativity.[40] The group also investigated the addition of venetoclax to cladribine, idarubicin, and cytarabine (CLIA), which proved safe in newly diagnosed patients without increased mortality and with durable MRD negativity.[41] Another venetoclax and intensive chemotherapy combination is the addition of venetoclax to "5+2" induction in older patients, which resulted in high remission rates and had an acceptable safety profile.[42] In a propensity-score analysis of trials combining venetoclax with intensive chemotherapy including anthracycline, purine analogues, and cytarabine, the addition of venetoclax led to high rates of MRD negativity compared to chemotherapy alone (86% *vs.* 61%; *P*=0.0028). A higher number of patients underwent allo-HCT in first remission in the venetoclax arms. Furthermore, the addition of venetoclax prolonged EFS (HR=0.57; 95% CI: 1.11-2.08; *P*=0.012).[43] The results of this *post-hoc* analysis are encouraging and should be confirmed by large prospective trials.

It is worth noting that relapse remains common with these regimens secondary to emerging resistance to venetoclax due to overexpression of MCL-1, gain of function of *FLT3*-ITD, or loss of function of *TP53*.[44] Combinations of a HMA with an *IDH-1/2* inhibitor, which are discussed below, have also been studied to investigate possible synergistic effects of these two types of drugs.

Hedgehog pathway inhibitor: glasdegib

The role of the Hedgehog signaling pathway in hematopoiesis is not clear. The pathway plays an essential role in cellular development and is fundamental in some carcinogenic pathways. Glasdegib is the only Hedgehog pathway inhibitor approved for use in AML, based on the results of the BRIGHT 1003 AML phase II trial evaluating the addition of glasdegib to LDAC in patients with AML/MDS unsuitable for intensive chemotherapy.[8] Eighty-eight and 44 patients were randomized to glasdegib-LDAC and LDAC, respectively. The median OS was 8.8 months in the combination group compared to 4.9 months in the LDAC group (HR=0.51, 80% CI: 0.39-0.67; *P*=0.0004). The CR rate was 17% *vs.* 2.3% (*P*<0.05) in the glasdegib-LDAC and LDAC arms, respectively. It is worth mentioning that this trial was criticized given that the results in the control arm (LDAC) were lower than those reported in previous studies. Nevertheless, this treatment provides an option for patients who are not eligible for intensive chemotherapy. Investigations of the combination of glasdegib with intensive chemotherapy (NCT03416179) with other novel treatments such as CPX-351 (NCT04231851) are underway.

Targetable mutations

Gene mutations are important in risk-stratification of AML. According to the European LeukemiaNet (ELN) 2017, the presence of a mutated *FLT3*-ITD or *TP53* is associated with worse outcomes.[45,46] On the other hand, mutations in *NPM1* without an *FLT3*-ITD mutation confer a survival advantage.[45,47] *IDH1/2* mutations were not described in the ELN 2017 risk stratification of AML and their prognostic significance is controversial, largely depending on co-occurring mutations.[48] As such, novel treatment has aimed at targeting detectable mutations.

FLT3 inhibitors. The utility of TKI has been established in both solid and hematologic malignancies. Given the negative prognostic influence of *FLT3*-ITD mutations, the therapeutic potential of TKI has been investigated in this context. Early or first-generation TKI, including midostaurin and sorafenib, are non-specific, targeting an array of TKI other than *FLT3*-ITD. Next-generation TKI include quizartinib, crenolanib, and gilteritinib, which are more specific and potent. Nevertheless, the relation of specificity to TKI and toxicity profile is not well understood. For example, quizartinib, a fairly specific, second-generation TKI is associated with high rates of toxicity, namely immunosuppression and QTc prolongation.[49]

Several TKI targeting *FLT3* have been evaluated in combination with intensive chemotherapy during induction treatment of AML. Sorafenib has been investigated for more than a decade. Ravandi *et al.* studied the outcome of patients with previously untreated AML who received a combination of sorafenib, cytarabine, and idarubicin, demonstrating a CR of 95% with an OS of 29 months.[50] In contrast, sorafenib combined with the standard "7+3" regimen did not improve OS or EFS in patients >60 years.[51] In patients aged <60 years, frontline sorafenib in combination with standard induction significantly prolonged EFS (21 *vs.* 9 months) and RFS (63 *vs.* 22 months) when compared to placebo combined with standard induction.[52] Recently, a phase II trial documented an improved OS but not EFS with sorafenib combined with intensive frontline chemotherapy, especially in patients with an allelic ratio >0.7.[53]

The RATIFY trial, central to the FDA approval of midostaurin for treating newly diagnosed *FLT3*-mutated (*FLT3*-ITD or *FLT3*-TKD) AML, highlighted improved survival in more than 700 patients aged <60 years, randomized to receive either placebo or midostaurin 50 mg orally twice daily on days 8-21 of each "7+3" cycle and high-dose cytarabine (HiDAC) consolidation.[2] Those in remission were also treated with daily midostaurin maintenance therapy for up to 1 year. EFS and 4-year OS were significantly improved in the midostaurin group (8.2 *vs.* 3 months and 51.4% *vs.* 44.2%, respectively).[2] Importantly, the group that received midostaurin had improved outcomes regardless of the subtype of *FLT3* mutation (TKD, ITD low allelic ratio or ITD high allelic ratio).[2]

The addition of crenolanib to the "7+3" regimen in patients <60 years has demonstrated tolerability and produced

Table 1. Trials with published results involving novel therapies in acute myeloid leukemia prior to allogeneic stem cell transplantation .

Trial	Drug	Study arms	Study design	Patient population, N	Median follow-up	Outcome	Study ID
				Induction			
				CPX-351			
Lancet *et al.*[1,31]	CPX-351 100 units/m²	CPX-351 *vs.* "7+3"	Open-label, phase III	309 patients: 60 to 75 years, untreated sAML Allo-HCT 92 patients	20.7 months	Improved OS: HR 0.69 (*P*=0.003) Allo-HCT: mOS: NR *vs.* 10.3 months; HR=0.51	NCT01696084
Issa *et al.*[33]	CPX-351 50, 75 and 100 units/m²	CPX-351 50 *vs.* 75 *vs.* 100 units/m²	Phase II	56 patients: newly diagnosed AML, unfit for intensive chemo Allo-HCT: 5 patients	27.8 months	OS: 4.5 (50 units/m²) *vs.* 8.6 (75 units/m²) *vs.* 6.2 (100 units/m²) *P*=0.04 Allo-HCT: mOS 13 *vs.* 12.4 months	NCT02286726
				Venetoclax			
DiNardo *et al.*[6]	VEN 400 mg	AZA/VEN *vs.* AZA/placebo	Phase III	431 patients: previously untreated AML	20.5 months	Improved OS: HR 0.66 (*P*<0.001)	NCT02993523
Wei *et al.*[7]	VEN 600 mg	LDAC/VEN *vs.* LDAC/placebo	Phase III	211 patients: untreated AML, unfit for intensive chemo	12 months	Improved OS: HR 0.4 (*P*=0.04)	NCT03069352
Reville *et al.*[41]	VEN 400 mg	Venetoclax 400 mg + CLIA	Phase II	50 patients: untreated AML Allo-HCT: 29 patients	13.5 months	94% composite CR, EFS and OS not reached Allo-HCT: not reported	NCT02115295
				FLT3 inhibitors			
Serve *et al.*[51]	Sorafenib 400 mg	Sorafenib + "7+3" *vs.* "7+3"	Phase III	211 patients: ≥60 years Allo-HCT: 4 patients with sorafenib *vs.* 3 patients with placebo	29.3 months	No statistically significant difference in CR	NCT00373373
Rollig *et al.*[52]	Sorafenib 400 mg	Sorafenib + "7+3" *vs.* "7+3"	Phase II	267 patients: ≤60 years, newly diagnosed AML Allo-HCT in CR1: 42 patients with sorafenib *vs.* 35 patients with placebo	36 months	Improved EFS: HR=0.64 (*P*=0.012) EFS not censored at allo-HCT: HR=0.66 (*P*=0.01)	NCT00893373
Wei *et al.*[53]	Sorafenib 400 mg	Sorafenib/IDA+Ara-C *vs.* placebo/IDA+Ara-C	Phase II	98 patients: newly diagnosed FLT3-mutated AML Allo-HCT in CR1: 62% (sorafenib) *vs.* 58% (placebo)	25 months	No improvement in EFS or ORR Allo-HCT: 2-year OS 78.5% (sorafenib) *vs.* 54.2% (placebo)	ACTRN126110011 2954
Stone *et al.*[2]	Midostaurin 50 mg twice daily	Midostaurin/"7+3" *vs.* placebo/"7+3"	Phase III	717 patients: FLT3-mutated AML Allo-HCT in CR1: 101 patients (midostaurin) *vs.* 81 patients (placebo)	19 months	Improved OS: HR=0.78 (*P*=0.008), improved EFS: HR=0.78 (*P*=0.001) No treatment effect was observed	NCT00651261
Goldberg *et al.*[55]	Crenolanib 100 mg TID	"7+3" + crenolanib	Phase II	27 patients: ≤60 years, newly diagnosed FLT3-mutated AML Allo-HCT: 20 patients	29.3 months	CR 85% Allo-HCT: similar survival allo-HCT *vs.* no allo-HCT	NCT02283177
Cortes *et al.*[49]	Quizartinib 60 mg QD	Quizartinib *vs.* SOC	Phase III	367 patients: R/R FLT3-mutated AML Allo-HCT: 78 patients with quizartinib 48 patients received quizartinib after allo-HCT	23.5 months	Improved OS: HR=0.76 (*P*=0.02)	NCT02039726

Trial	Drug	Study arms	Study design	Patient population, N	Median follow-up	Outcome	Study ID
Induction							
Perl *et al.*[59]	Gilteritinib 120 QD	Gilteritinib *vs.* SOC	Phase III	371 patients: R/R *FLT3*-mutated AML	17.8 months	Improved OS: HR=0.64 (*P*<0.001)	NCT02421939
IDH1/2 inhibitors							
Pollyea *et al.*[69]	Enasidenib 50-650 mg/day	Enasidenib	Phase I/II	39 patients: newly diagnosed *IDH2*-mutated AML, unfit for intensive chemo Allo-HCT: 3 patients	8.4 months	ORR 30.8%, 18% CR, OS 11.3 months Allo-HCT: 3 patients alive and in CR, 28, 32, and 38 months after allo-HCT	NCT01915498
DiNardo *et al.*[4]	Enasidenib 100 or 200 mg/day	Enasidenib/AZA *vs.* AZA	Phase I/II	107 patients: newly diagnosed *IDH2*-mutated AML	12 months	Improved ORR: OR 4.9 (*P*=0.0003)	NCT02677922
Roboz *et al.*[70]	Ivosidenib 500 mg/day	Ivosidenib	Phase I	34 patients: newly diagnosed *IDH1*-mutated AML, unfit for intensive chemo Allo-HCT: 3 patients	23.5 months	CR 30.3%, OS 12.6 months	NCT02074839
Stein *et al.*[71]	Ivosidenib 500 mg or Enasidenib 100 mg	IVO/enasidenib + chemo	Phase I	60 patients in the IVO cohort, 93 in the ENA cohort, newly diagnosed AML Allo-HCT: 28 patients (IVO) *vs.* 43 patients (ENA)	IVO: 9.3 months ENA: 14.5 months	CR/CRi/CRp rates: 77% (ivosidenib) and 74% (enasidenib)	NCT02632708
DiNardo *et al.*[4]	Ivosidenib 500 mg/day	Ivosidenib + AZA	Phase Ib	23 patients: newly diagnosed AML	16 months	ORR 78.3%, CR 60.9%	NCT02677922
Montesinos *et al.*[74]	Ivosidenib 500 mg/day	Ivosidenib/AZA *vs.* placebo/AZA	Phase III	146 months: *IDH1*-mutated AML	12.4 months	Improved EFS: HR=0.69 (*P*=0.002)	NCT03173248
APR-246							
Sallman *et al.*[81]	Eprenetapopt 50, 75, 100 mg/kg	Eprenetapopt + AZA	Phase I/II	55 patients: *TP53*-mutated AML/MDS (11 high-risk AML) Allo-HCT: 19 patients	10.5 months	ORR in AML 58%, CR 36%	NCT03072043
Hedgehog inhibitors							
Cortes *et al.*[8]	Glasdegib 100 mg	Glasdegib/LDAC *vs.* LDAC	Phase II	132 patients: AML/MDS, unfit for intensive chemo	21.7 months	Improved OS: HR=0.51 (*P*=0.0004)	NCT01546038
Gemtuzumab ozogamicin							
Petersdorf *et al.*[23]	GO 6 mg/m²	GO/"7+3 "*vs.* "7+3"	Phase III	595 younger AML patients Allo-HCT: 43 patients	30 months	No improvement in CR, EFS, OS	NCT00085709

AML: acute myelogenous leukemia; Allo-HCT: allogeneic hematopoietic cell transplantation; OS: overall survival; HR: hazard ratio; VEN: venetoclax; AZA: azacitidine; *vs: versus*; LDAC: low-dose cytarabine; CLIA: cladribine, idarubicin, and high-dose cytarabine; CR: complete remission; EFS: event-free survival; IDA+ara-c: idarubicin and cytarabine; R/R: relapsed and refractory; ORR: overall response rate; SOC: standard of care; CC: conventional chemotherapy; ENA: enasidenib; IVO: ivosidenib; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; MDS: myelodysplastic syndrome; GO: gemtuzumab ozogamicin; RIC: reduced intensity conditioning; NMA: non-myeloablative; MPN: myeloproliferative neoplasm; PFS: progression-free survival; RFS: relapse-free survival; NRM: non-relapse mortality; TBI: total body irradiation; G-CSF: granulocyte colony-stimulating factor; G-Dec: G-CSF and decitabine; DLT: dose-limiting toxicity

promising outcomes in a phase II study.[54] Importantly, its use in patients with mutations other than *FLT3* has demonstrated that the addition of crenolanib can overcome the poor prognosis implied by other concurrent mutations.[55] Quizartinib, even as monotherapy, has produced significant remissions in R/R, *FLT3*-mutated AML.[56] A phase III trial, QuANTUM-R, evaluated quizartinib monotherapy *versus* investigator choice of treatment in R/R *FLT3*-ITD AML. The OS associated with quizartinib monotherapy was 6.2 months compared to 4.7 months for the other patients (HR=0.76; *P*=0.02).[49] Long-term follow-up of the trial confirmed the results (HR for OS=0.776; *P*=0.324).[57] Although positive, QuANTUM-R results were strongly criticized by the FDA, thus leading to the drug not being approved. This was due to the reported improved OS, which correlated with a median survival extended by only 6 weeks without a significant improvement in EFS. Furthermore, the dropout rate from the chemotherapy arm was much higher (23% *vs.* 11%) and more patients treated with quizartinib underwent HCT (32% *vs.* 11%), further confounding the results.[58] The phase III trial, ADMIRAL, evaluated monotherapy with gilteritinib *versus* investigator choice of treatment in the same population: treatment with gilteritinib improved OS from 5.6 to 9.3 months (*P*<0.001), which led to its approval in the USA and Europe for treatment of this patient population.[59]

Currently, midostaurin remains the only approved TKI for treating previously untreated *FLT3*-mutated AML. Midostaurin *versus* gilteritinib in combination with induction and consolidation in newly diagnosed *FLT3*-mutated AML is being explored in the HOVON 156 AML trial (NCT04027309). The frontline use of quizartinib in combination with the "7+3" regimen is being investigated in the phase III, double-blind, placebo-controlled QuANTUM-First trial (NCT02668653). Another phase III study is currently comparing crenolanib *versus* midostaurin when added to the "7+3" regimen in newly diagnosed *FLT3*-mutated AML (NCT03258931).[60] The results of these two trials could change treatment guidelines for this challenging patient population. Quizartinib is also being evaluated in combination with CPX-351 (NCT04209725) and with CLIA (NCT04047641) in untreated and R/R *FLT3*-mutated AML. The addition of *FLT3*-TKI to low-intensity treatment was also studied in patients not eligible for chemotherapy. Sorafenib was added to azacitidine in a phase II trial, showing efficacy in patients with relapsed *FLT3*-ITD-positive AML.[61] Sorafenib was studied in the frontline setting in another phase II trial in combination with azacitidine. Most of the patients were 60 years or older. The combination was both well tolerated and effective.[62] Another *FLT3* inhibitor, gilteritinib, was added to azacitidine and the combination compared to azacitidine monotherapy (NCT02752035) in the LACEWING phase III trial in the first-line setting.[3] Midostaurin was assessed in combination

with azacitidine in newly diagnosed and R/R AML in a phase I/II trial.[63] Quizartinib was combined with azacitidine or LDAC in untreated and R/R AML in a phase I/II trial.[64] Except for the last trial which showed acceptable CR and OS rates, *FLT3*-TKI alone or in combination with HMA or LDAC did not markedly change the outcomes of patients with *FLT3*-mutated AML not eligible for intensive chemotherapy. This could be largely due to an escape mechanism through which leukemic cells develop resistance to treatment. One of the mechanisms of resistance is the upregulation of BCL-2 receptors.[65] Based on this finding, several ongoing studies are assessing the use of doublet or triplet combinations of *FLT3*-TKI and venetoclax. In a phase I/II trial presented at the American Society of Hematology annual meeting in 2021, gilteritinib was combined with venetclax and azacitidine for the treatment of newly diagnosed or R/R *FLT3*-mutated AML. Two doses were studied and 80 mg was chosen for a phase II trial based on dose-limiting toxicities observed with the 120 mg dose. Even at the 80 mg dose, the triplet combination was associated with marked myelosuppression requiring dose adjustments of azacitidine and venetoclax.[66] Nevertheless the efficacy of this triplet combination is promising, with a high CR rate of 100% and 67% in the frontline and R/R AML setting, respectively.

IDH-1/2 inhibitors. *IDH-1* and *IDH-2* are critical for the oxidative carboxylation of isocitrate. Mutations in these enzymes result in the accumulation of 2-hydroxyglutyrate, causing DNA and histone hypermethylation, cellular differentiation arrest, and tumorigenesis. Such mutations account for 15% of newly diagnosed AML.[67] Oral inhibitors of mutant *IDH-1* (ivosidenib) and *IDH-2* (enasidenib) have been explored in the frontline and R/R settings. In the R/R setting, the FDA approved the two drugs as monotherapy for the corresponding mutation, given promising results of ivosidenib and enasidenib with overall response rates of 41.6% and 40.3%, and median OS of 8.8 and 9.3 months, respectively.[4,68] In the frontline setting, both inhibitors were also approved by the FDA for the treatment of older patients ineligible for intensive chemotherapy.[69,70] Stein *et al.* studied the addition of either *IDH* inhibitor to the "7+3" regimen in patients with *de novo* *IDH*-mutated AML. Sixty had mutant *IDH-1* and received ivosidenib, among whom the response rate was 93% and 1-year OS 79%. Ninety-one had mutated *IDH-2* and received enasidenib, among whom the overall response rate was 73% and OS 75%.[71]

Combinations of *IDH* inhibitors with the previously discussed HMA have been explored. Ivosidenib combined with azacitidine was studied as frontline therapy in 23 patients with *IDH*-mutated AML: the overall response rate was 78% and the CR rate was 70%, with a median time to response of 1.8 months. *IDH*-mutation clearance was seen in 63% of the patients achieving a CR. Out-

Table 2. Trials with published results involving novel therapies in acute myeloid leukemia during and after allogeneic stem cell transplantation.

Trial	Drug	Study arms	Study design	Patient population, N	Median follow-up	Outcome	Study ID
Conditioning							
Treosulfan							
Casper J *et al.*[93]	Treosulfan 10 or 12 or 14 mg/m² for 3 days	Treosulfan + fludarabine	Phase II	56 patients with hematologic malignancies (19 with AML)	24 months	OS 64%, PFS 49%, Relapse/progression 31%	NCT01063647
Lazzari L. *et al.*[94] AlloTreo	Treosulfan 14 mg/m² for 3 days	Treosulfan + fludarabine	Phase II, open-label, non-randomized	108 patients with hematologic diseases	12 years	OS 41.7%, PFS 31.7%, cumulative incidence of relapse 44.5% (high)	NCT00598624
Stölzel F *et al.*[96] MC-FludT.14/L	Treosulfan 10 mg/m² for 3 days	Treosulfan/fludarabine *vs.* Busulfan/fludarabine (RIC)	Phase III, non-inferiority	352 patients with AML	15.4 months (treosulfan) 17.4 months (busulfan)	2-year EFS 64% (treosulfan) and 50.4% (busulfan) (*P*<0.0001)	NCT00822393
Venetoclax							
Garcia *et al.*[97]	Venetoclax 200-400 mg starting day -8 for 6-7 days	Venetoclax + RIC busulfan + fludarabine	Phase I	22 patients with high-risk AML, MDS, MPN	14.7 months	RP2D 400 mg, mOS not reached, mPFS 12.2 months	NCT03613532
Popat *et al*[98]	Venetoclax 400 mg, day -22 to -3	Venetoclax + MAC frac busulfan + fludarabine + cladribine	Phase II	33 patients with AML or MDS	8 months	1-year OS 84%, 1-year PFS 77%, relapse 13%, NRM 10%	NCT02250937
FLT3 inhibitors							
Popat *et al.*[99]	Sorafenib 200 mg or 400 mg or 600 mg or 800 mg	Sorafenib + MAC frac busulfan + fludarabine	Phase I	24 patients with AML	7.6 months	RP2D 800 mg, 1-year OS 86%, 1-year PFS 89%	NCT03247088
Anti-CD117							
Muffly *et al.*[100]	Anti-CD117 (c-KIT) monoclonal antibody, JSP191	JSP191 + NMA fludarabine + TBI	Phase I	24 patients with AML or MDS	6 months	Neutrophil engraftment: day 19-26, morphological relapse in 4 patients	NCT04429191
Targeted radiation therapy with anti-CD45							
SIERRA trial[90, 102]	Iomab-B	Iomab-B + RIC (Fludarabine + TBI) *vs.* CC	Phase III	136 patients with R/R AML		CC arm: 52 non-responders, 38/52 cross-over to Iomab-B arm, median neutrophil engraftment in Iomab arm: 14 days, platelets 18 days, febrile neutropenia: 37% (Iomab) *vs.* 50% (CC), mucositis 10% (Iomab) *vs.* 20% (CC)	NCT02665065
Maintenance							
Hypomethylating agents							
de Lima *et al.*[109]	AZA 8, 16, 24, 32, and 40 mg/m², day +40	AZA *vs.* Placebo	Phase III	N=45, high-risk AML or MDS	20.5 months	RP2D 32 mg/m², 1-year EFS 58% and 2-year OS 77%	NCT00350818
Oran *et al.*[111]	AZA 32 mg/m² x5 every 28 days, for 1 year	AZA *vs.* Observation	Phase III	N=187, AML or MDS	4.6 years (AZA) 4.06 years (placebo)	No difference: mRFS 2.07 years *vs.* 1.28 years, *P*=0.43, mOS 2.52 years *vs.* 2.56 years, *P*=0.85	NCT00887068
Pusic *et al.*[115]	Decitabine 5-15 mg/m² for 5 days every 6 weeks, day +50 to +100	No comparator arm	Phase I	N=24, AML	26.7 months	RP2D 15 mg/m², 2-year OS: 56%, 2-year RFS: 48%, aGVHD: 41%, cGVHD: 63%	NCT00986804

Trial	Drug	Study arms	Study design	Patient population, N	Median follow-up	Outcome	Study ID
Gao *et al.*[116]	Decitabine 5 mg/m² ×5 days + G-CSF	G-Dec *vs.* no-intervention	Phase II	N=204, high-risk AML	28 months	Cumulative incidence of relapse 15% (G-Dec) *vs.* 38% no-intervention, 2-year OS 85.8% (G-Dec) *vs.* 69.7% (non–G-Dec), *P*= 0.01	ChiCTR-IIR-16008182
Venetoclax							
Kent *et al.*[118]	Venetoclax 400 mg for 1 year	No comparator arm	Cohort study	23 patients with high-risk AML or MDS	219 days	6-months OS and PFS 87%	
Wei *et al.*[119]	Venetoclax 200 mg/day x21+low-dose decitabine 15 mg/m² x3, day +100	No comparator arm	Phase II	20 patients with high-risk AML or MDS	598 days	2-year OS 85.2%, 2-year EFS 84.7%, 100-day aGVHD 55%, 100-day cGVHD 20%	ChiCTR1900025374
***FLT3* inhibitors**							
Burchert *et al.*[112] Sormain trial	Sorafenib	Sorafenib *vs.* placebo	Phase II	83 patients with *FLT3*-mutated AML	41.8 months	HR for relapse=0.39, *P*=0.013, 24-month RFS 53.3% (placebo) *vs.* 85.0% (sorafenib), *P*=0.002	DRKS00000591
Maziarz *et al.*[124] Radius trial	Midostaurin	Midostaurin *vs.* SOC	Phase II	60 patients with *FLT3*-mutated AML	24 months	18-month RFS 89% (midostaurin) *vs.* 76% (SOC), *P*=0.27; relapse rates 11% (midostaurin) *vs.* 24% (SOC)	NCT01883362
APR-246 (Eprenetapopt)							
Mishra *et al.*[128]	Eprenetapopt 3.7 g/day x 4 + azacitidine 36 mg/m²/day x5	No comparator arm	Phase II	33 patients with TP53-mutated AML or MDS	429 days	1-year OS 79%, 1-year RFS 58%	NCT03931291
Histone deacetylase inhibitors							
Bug *et al.*[130] PANOBEST trial	Panobinostat, day +96	20 mg once a week or 30 mg every other week	Phase I/II	42 patients, AML or MDS	22 months	2-year OS 81%, 2-year RFS 75%, 2-year cGVHD 29%	NCT01451268
Immunotherapy							
Devillier *et al.*[132]	Monalizumab 0.04, 0.1, 0.3, 1 mg/kg	No comparator arm	Phase I	15 patients with hematologic malignancies (9 with AML)	22 months	No disease recurrence, DLT 1 mg/kg, 13/15 in CR and no GVHD	NCT02921685

AML: acute myelogenous leukemia; Allo-HCT: allogeneic hematopoietic cell transplantation; OS: overall survival; HR: hazard ratio; VEN: venetoclax; AZA: azacitidine; *vs*: versus; CR: complete remission; EFS: event-free survival; R/R: relapsed and refractory; ORR: overall response rate; CRi: complete remission with incomplete hematologic recovery; CRp: complete remission with incomplete platelet recovery; MDS: myelodysplastic syndrome; RIC: reduced-intensity conditioning; NMA: nonmyeloablative; MPN: myeloproliferative neoplasm; PFS: progression-free survival; RFS: relapse-free survival; NRM: non-relapse mortality; TBI: total body irradiation; G-CSF: granulocyte colony stimulating factor; aGVHD and cGVHD : acute and chronic graft-*versus*-host disease; G-Dec: G-CSF and decitabine; DLT: dose-limiting toxicity; RP2D: recommended phase II dose.

comes surpassed those expected with azacitidine alone.[72,73] The recently published phase III AGILE trial (NCT03173248) compared azacitidine-ivosidenib and azacitidine-placebo in patients with untreated *IDH1*-mutated AML, ineligible for intensive chemotherapy.[74] At a median follow-up of 12.4 months, EFS was significantly better in the combination group (HR=0.33; *P*=0.002).[74] The median OS was 24 months *versus* 7.9 months in the azacitidine-ivosidenib and azacitidine-placebo groups, respectively (HR=0.44; *P*=0.001).[74] These results led to FDA approval of the azacitidine-ivosidenib combination in patients >75 years or unfit for intensive chemotherapy in May 2022. Similarly, enasidenib combined with azacitidine has been studied in a phase Ib/II study with recently published results. One hundred and one patients (median age of 75 years) were randomized 2:1 to receive azacitidine-enasidenib or azacitidine alone. The overall response rate improved significantly from 36% to 74% in the combination group (OR=4.9; *P*=0.0003), but the study failed to show any survival difference with the combination.[5] This finding could have been confounded by the subsequent use of salvage enasidenib in the azacitidine-only arm. A large, phase III trial is underway to investigate the impact of adding ivosidenib or enasidenib *versus* placebo to induction and maintenance therapy in *IDH*-mutated AML patients eligible for intensive chemotherapy (NCT03839771).

TP53-targeting agents. *TP53* mutations occur in up to 20% of patients, are usually associated with complex/monosomal karyotype, and are more common in older patients with therapy-related AML.[75] They invariably confer resistance to conventional therapeutic approaches in most patients harboring such mutations.[76] Eprenetapopt (APR-246) is a novel agent that could restore activity to mutant p53, thus inducing apoptosis of cancer cells.[77] A phase Ib/II study (NCT03072043) investigated the safety and efficacy of adding eprenetapopt to azacitidine in 55 patients with *TP53*-mutated AML/MDS, in whom the overall response rate and CR in AML patients were 64% and 36%, respectively.[10] OS in responding patients improved significantly (14.6 *vs.* 7.5 months; *P*=0.0005), and adverse events were those expected with azacitidine or eprenetapopt alone (febrile neutropenia, leukopenia).[10] This combination was explored independently by the Groupe Francophone des Myelodysplasies in a phase II study (NCT03588078) of 52 *TP53*-mutated patients, of whom 18 had AML; the overall response rate and CR rates were 33% and 17%, respectively.[78] These two studies highlighted the potential safety and benefit of combining eprenetapopt with azacitidine compared to azacitidine alone. The outcomes of patients with *TP53*-mutated AML remain poor, and no regimen has improved OS in those patients, including decitabine (10 days)/venetoclax.[79]

Immunotherapy
Magrolimab (Hu5F9-G4). CD47 has been studied as another potential target for treating AML, specifically in patients who are unfit for high-intensity therapy. The upregulation of CD47 in AML allows tumor cells to evade destruction by macrophages, an effect independently associated with a poor prognosis.[80] Hu5F9-G4 (magrolimab) is a monoclonal antibody that binds to CD47, leading to phagocytic elimination of tumor cells. The combination of magrolimab and azacitidine was evaluated in 34 patients with AML or intermediate-high risk MDS, in whom the overall response rate was 65% (CR, 40%).[81] Interestingly, among patients with abnormal cytogenetics, 47% achieved a complete cytogenetic response. Among those with concurrently mutated *TP53*, the overall response rate was 71% (CR, 48%); these patients had a median OS of 12.9 months compared to 18.9 months in patients with *TP53* wild-type AML.[81] Thus, targeting CD47 without targeting mutated *TP53* in this group resulted in favorable outcomes, paving the way for future trials involving the novel monoclonal antibody. There are currently two trials investigating the three-drug combination of magrolimab with venetoclax and azacitidine (NCT05079230 and NCT04435691). In addition, magrolimab-azacitidine is being compared to venetoclax-azacitidine *versus* intensive chemotherapy alone in previously untreated TP53-mutated AML in a phase III trial (NCT04778397).

Impact of minimal residual disease on the outcomes of allogeneic hematopoietic cell transplantation

Evaluation of MRD before and after allo-HCT is of clinical interest with the aim of tailoring patients' treatment prior to allo-HCT based on their individual risks and identifying and treating patients who are MRD-positive after transplantation before any clinical relapse. Patients who are MRD-positive by multiparametric flow cytometry at the time of allo-HCT were shown to have an increased risk of relapse and decreased leukemia-free survival and OS.[82] In an analysis of EBMT registry data, the presence of detectable *IDH1-2* mutations prior to transplantation significantly increased the risk of relapse.[83] In the HOVON-SAKK-132 phase III trial, patients with AML received consolidation with allo-HCT based on an MRD-adapted approach. Patients received induction chemotherapy with or without lenalidomide.[84] After two cycles of induction, patients were randomized, based on baseline risk and MRD status, to a third cycle of induction (favorable-risk cases), autologous stem cell transplantation (intermediate-risk and MRD-negative cases), or allo-HCT (intermediate-risk and MRD-positive or unknown, or high-risk cases). The out-

come of patients with intermediate-risk disease was similar for patients with MRD-negative or positive disease (4 -year RFS: 50% in MRD-positive cases *vs.* 52% in MRD-negative cases, HR=1.18, *P*=059; 4-year OS: 64% in MRD-positive cases *vs.* 69% in MRD-negative cases, HR=1.31, *P*=0.46).[84] These results indicate that MRD-directed therapy could help to avoid allo-HCT in patients with intermediate-risk AML who are MRD negative prior to transplantation. However, patients stratified into the intermediate-risk group harbor diverse mutations and assessment of the role of MRD on the decision to perform allo-HCT should be studied in those different subgroups. A particular question that should be addressed is the impact of addition of targeted agents to induction treatment and the impact of MRD on the decision to perform allo-HCT, specifically in the era of maintenance therapy. In the post-allo-HCT setting, Shah *et al.* found that detection of MRD by multiparametric flow cytometry early after allo-HCT predicted relapse (within 2 months) and led to better risk-stratification of patients with AML after transplantation.[85] This highlights the need for preventive measures to avoid relapses, discussed later in this review. In summary, MRD-directed therapy could be potentially used for treatment guidance for patients with AML; however, its impact on transplant decisions has not yet been established, especially in patients with intermediate-risk AML who become MRD-negative after transplantation. Similarly, post-allo-HCT MRD should be used to direct maintenance therapy.

Novel approaches in allogeneic hematopoietic cell transplantation for acute myeloid leukemia

While numerous novel therapies are emerging, allo-HCT remains the standard of care for patients with ELN 2017 intermediate- and adverse-risk disease in first CR.[46] Based on the results of the BMT CTN 0901 randomized phase III trial, there is clear evidence that myeloablative conditioning (MAC) improves OS in patients with AML or MDS undergoing allo-HCT compared to RIC (HR=1.54; 95% CI: 1.07-2.2; *P*=0.03).[86] Although RIC increases the risk of relapse, it is associated with reduced toxicity, leading to lower treatment-related mortality compared to MAC (9.9% *vs.* 25.1%; *P*<0.01), broadening the use of allo-HCT in the older population.[86,87] However, the optimal conditioning therapy would be a regimen that carries lower risk of toxicity and treatment-related mortality but retains cytoreductive properties and, ideally, does not affect outcomes, a regimen that was recently described as "reduced toxicity conditioning".[88]

Another unmet need is transplantation for refractory leukemia. Sequential approaches are conditioning plat-

forms developed for patients with refractory or active AML. These regimens have two phases of therapy; induction chemotherapy that targets refractory leukemia followed by RIC, relying mainly on the graft-*versus*-leukemia (GvL) effect. FLAMSA (fludarabine, cytarabine, and amsacrine, followed by 4 Gy of total body irradiation, cyclophosphamide, and an anti-thymocyte globulin) was the first "sequential regimen" developed. More recently FLAMSA-like combinations have emerged.[89] Other conditioning regimens recently developed for allo-HCT of active or refractory AML include targeted radiation therapy using anti-CD45 monoclonal antibody (Table 2 and Table 3).[90] Novel therapies for use in AML during and after allo-HCT are secribed below. Those for which results have been published are summarized in Table 2. Table 3 lists ongoing trials involving novel therapies for AML before, during and after allo-HCT.

Treosulfan-based conditioning regimens

Busulfan is an alkylating agent with an erratic gastrointestinal absorption needing multiple daily oral or targeted intravenous dosing.[91] It is associated with toxicity, mainly veno-occlusive disease and idiopathic pulmonary syndrome.[92] Treosulfan is a bifunctional alkylating prodrug with myeloablative properties and a reduced non-hematologic toxicity profile. It is administered intravenously, but drug levels do not need to be monitored because it does not have dose-limiting organ toxicity.[93] In a dose-finding study, treosulfan was evaluated in combination with fludarabine in patients with hematologic malignancies undergoing allo-HCT. There was no dose-limiting toxicity, and the final dose chosen for further studies was 14 g/m^2 x3.[93] Another phase II open-label, non-randomized trial (AlloTreo) evaluated the safety and efficacy of treosulfan (42 g/m^2) with fludarabine in patients with hematologic malignancies undergoing first allo-HCT. Anti-thymocyte globulin was added to the conditioning regimen in patients undergoing unrelated donor transplants. After 12 years of follow-up, OS and PFS were 41.7% and 31.7%, respectively. The cumulative incidence of relapse was high at 44.5%. This could be explained by the higher disease risk of patients included in the study.[94] To confirm these findings, a phase III, open-label, non-inferiority trial (MC-FludT.14/L) was conducted comparing treosulfan/fludarabine (FT10) to RIC fludarabine/busulfan in patients ≥50 years or with comorbidities. Treosulfan was given at a dose of 10 mg/m^2 for 3 days. The study included 476 patients with AML or MDS. The median follow-up was 15.4 and 17.4 months for treosulfan- and busulfan-based conditioning, respectively. The 2-year EFS was higher in the treosulfan arm (64%) than in the busulfan arm (50.4%) (*P*<0.0001). Both drugs had similar hematologic toxicity rates (15%); however, treosulfan was associated

with a lower risk of gastrointestinal toxicity (11% *vs*. 16%). This trial has shown that treosulfan is non-inferior to busulfan in older patients or those with comorbidities. Based on this study, treosulfan was approved by the EMA at a dose of 30 mg/m^2 for malignant diseases.[95] A subgroup analysis of patients with AML was presented at the Tandem ASTCT and CIBMTR meetings in 2022: EFS, OS, and graft-*versus*-host disease (GvHD)-free, relapse/progression-free survival were significantly higher in the treosulfan group (64.7% *vs*. 53.3%, *P*=0.01; 72.8% *vs*. 64.7% *P*=0.03; and 52.9% *vs*. 39.6%, *P*=0.02, respectively).[96] These

results support the use of treosulfan rather than busulfan in patients not eligible for standard MAC.

Addition of targeted therapy to standard conditioning regimens
BCL-2 inhibitors
As mentioned earlier, the use of venetoclax has improved the outcomes of patients with AML in the frontline and R/R settings.[6] A phase I dose-escalation study assessed the addition of venetoclax to RIC fludarabine/busulfan in adult patients with AML or MDS undergoing allo-HCT.[97] Pa-

Table 3. Ongoing trials involving novel therapies in acute myeloid leukemia before, during, and after allogeneic stem cell transplantation.

Study	Description	Intervention	Population
Induction			
NCT05024552	Phase I	CPX-351 + Gilteritinib	R/R, *FLT3*-mutated AML
NCT04128748	Phase Ib/IIa	CPX-351 + Quizartinib	Frontline cohort: >60 years, previously untreated AML/MDS; R/R cohort: >18 years
NCT03904251	Phase I	CPX-351 + Gemtuzumab	Relapsed AML
NCT03878927	Phase I	CPX-351 + Gemtuzumab	>55 years with AML
NCT04425655	Phase II	CPX-351 + Fludarabine	Intermediate- or poor-risk AML
NCT04038437	Phase I	CPX-351 + Venetoclax	Newly diagnosed AML
NCT03844997	Phase Ib/IIa	CPX-351 + Palbociclib	Newly diagnosed AML
NCT04231851	Phase II	CPX-351 + Glasdegib	Previously untreated therapy-related AML
NCT02668653	Phase III	"7+3" + Quizartinib *vs*. "7+3" + Placebo	Newly diagnosed AML
NCT03258931	Phase III	Crenolanib *vs*. Midostaurin	Newly diagnosed *FLT3*-mutated AML
NCT03839771	Phase III	Ivosidenib/enasidenib *vs*. Placebo	Newly diagnosed *IDH-1/2* mutated AML
NCT04435691	Phase Ib/IIa	Magrolimab/azacitidine/venetoclax	R/R AML, not eligible for salvage chemotherapy or HCT
NCT05079230	Phase III	Magrolimab/azacitidine/venetoclax *vs*. Placebo/azacitidine/venetoclax	Newly diagnosed AML, ineligible for standard "7+3"
NCT04778397	Phase III	Magrolimab/azacitidine *vs*. venetoclax/azacitidine	Newly diagnosed, *TP53*-mutated AML
Conditioning regimen			
NCT04195633	Phase II	Treosulfan + Fludarabine + TBI	Adult patients with hematologic malignancies
NCT03613532	Phase I	Venetoclax + Fludarabine + Busulfan	Patients with AML/MDS
NCT03247088	Phase I/II	Sorafenib + Busulfan + Fludarabine	R/R AML
NCT02250937	Phase II	Venetoclax + Sequential Busulfan + Fludarabine + Cladribine	Patients with AML/MDS
NCT04429191	Phase I	Anti-CD117, JSP191	Patients with AML or MDS
NCT05139004	Phase I	90Y-DOTA-anti-CD25, basiliximab	Patients with high-risk AML/MDS
Post-allo-HCT maintenance			
NCT03613532	Phase I	Venetoclax + Azacitidine	Patients with AML/MDS
NCT02997202	BMT-CTN 1506 phase III	Gilteritinib *vs*. Placebo	*FLT3*-ITD-mutated AML
NCT03564821	Phase I	Ivosidenib	*IDH1*-mutant myeloid neoplasms
NCT03515512	Phase I	Enasidenib	*IDH2*-mutant myeloid neoplasms
NCT03728335	Phase I	Enasidenib	*IDH2*-mutant myeloid neoplasms
NCT04522895	Phase II	Enasidenib	*IDH2*-mutated MDS, CMML and AML
NCT04326764	ETAL-4 / HOVON-145 phase III	Panobinostat *vs*. SOC	High-risk AML or MDS

R/R: relapsed and refractory; AML: acute myelogenous leukemia; MDS: myelodysplastic syndrome; HCT: hematopoietic stem cell transplantation; TBI: total body irradiation; SOC: standard of care; CMML: chronic myelomonocytic leukemia.

tients received venetoclax at a dose of 200-400 mg starting on day -8 for 6-7 days. A total of 22 patients were included. Acute GvHD was observed in 12/22 patients, with one patient having grade III acute GvHD. The median time to neutrophil engraftment was 15 days, similar to that observed with RIC fludarabine/busulfan. No dose-limiting toxicity was reported; hence, the dose of 400 mg was chosen for the phase II trial.[97] A phase II trial assessed the addition of venetoclax to myeloablative fractionated busulfan, fludarabine, and cladribine conditioning in patients with AML or MDS. The authors hypothesized that adding venetoclax might be synergistic with chemotherapy. The study included 33 patients (AML, n=21; MDS, n=10) up to 70 years of age. Venetoclax was administered at a daily dose of 400 mg from day -22 to -3 without azoles. The 1-year OS, PFS, relapse, and NRM rates were 84%, 77%, 13%, and 10%, respectively. The median time to neutrophil and platelet engraftment was 15 and 23 days, respectively. The most common grade ≥3 adverse events were febrile neutropenia (58%), mucositis (18%), and pulmonary toxicity (21%). The day 100 grade II-IV acute GvHD rate was low at 3%.[98] These results showed that adding venetoclax to the conditioning regimen was safe, did not affect engraftment, and had promising early outcome results.

FLT3-inhibitors

Another targeted agent added to a conditioning regimen was a first-generation *FLT3*-TKI, investigated in a phase I study presented at the Tandem meetings in 2022, in which sorafenib was added to MAC fractionated busulfan/fludarabine.[99] Twenty-four patients with AML were included. Sorafenib was added from day -24 to -5 at different dose levels (200, 400, 600, and 800 mg). The dose of 800 mg was recommended for the phase II study. The 1-year OS and PFS rates for all patients were 86% and 89%, respectively. The grade II-IV and grade III-IV acute GvHD rates at day 100 were 54% and 5%, respectively. These results show that sorafenib can be safely added to the fractionated busulfan regimen, although longer follow-up and larger studies are needed for a more complete evaluation.

Anti-CD117 monoclonal antibody

An anti-CD117 (c-KIT) monoclonal antibody, JSP191 was added to non-MAC consisting of low-dose total body irradiation and fludarabine. JSP191 depletes both hematopoietic stem cells and leukemic cells and synergizes with total body irradiation and fludarabine facilitating engraftment.[100] The phase I study reporting the outcomes of 17 patients was presented at the Tandem meetings in 2022. The combination was safe without any infusion or serious adverse effects observed. Neutrophil engraftment occurred between day 19 and day 26. Only one grade 2-4 side effect was observed. Donor chimerism was evaluated in 14 patients at day 90; all of them had full myeloid donor chimerism. High rates of MRD clearance were observed in 15/17 subjects who were MRD-positive at the time of transplantation. These results are promising especially with the use of non-myeloablative allo-HCT. The study is ongoing and final results are awaited (NCT04429191).

Sequential approach in relapsed/refractory patients and those transplanted in active disease

Given the low response rates and short survival of patients with refractory leukemia, allo-HCT remains the only option of cure. However, MAC is associated with a high treatment-related mortality of around 40% and RIC, although it decreases treatment-related mortality, is insufficient to control refractory leukemia alone through the GvL effect.[89,101] A sequential approach was developed through the addition of a short course of intensive chemotherapy prior to RIC with the aim of reducing the disease burden and enhancing the GvL effect. The first sequential regimen developed was the FLAMSA regimen which was associated with high toxicity mainly related to amsacrine and total body irradiation. Another sequential regimen published by Duléry *et al.* was the TEC-RIC regimen (thiotepa, etoposide, cyclophosphamide followed by RIC of fludarabine, busulfan, and anti-thymocyte globulin). Sixty-one percent of the patients had AML. Results were promising, with 2-year OS and EFS rates of 54.7% and 49.3%, 49.2% and 43.8%, 37.9%, and 28%, in haploidentical, related, and unrelated donor transplants, respectively. Mucositis and gut toxicities were the most common toxicities observed.[89] These results indicated the safety and efficacy of the TEC-RIC sequential approach in allo-HCT for active or refractory AML.

Targeted radiation therapy with an anti-CD45 monoclonal antibody (Iomab-B)

Many patients with active R/R AML are not fit for intensive chemotherapy or MAC, making them ineligible for sequential approaches. The SIERRA trial (Study for Iomab-B in Elderly Relapsed or Refractory AML) investigated using Iomab-B, a ^{131}I-labeled anti-CD45 monoclonal antibody, as conditioning prior to allo-HCT.[90,102] Patients were randomized to receive Iomab-B followed by fludarabine and low-dose total body irradiation, or conventional care. The median age of the participants was 65 years. The rate of allo-HCT was higher in the Iomab-B arm (90%) than in the conventional care arm (17%). Patients who did not achieve CR in the conventional care arm could cross over to the Iomab-B arm. Median times of neutrophil and platelet engraftment were 14 and 18 days, respectively. Patients enrolled in the Iomab-B arm had a significantly lower incidence of grade ≥3 side effects compared to those in the conventional care arm (5% *vs.* 30%; *P*<0.05), with these side effects being mainly sepsis and mucositis. These data

show that the Iomab-B-based conditioning regimen is safe and associated with acceptable engraftment kinetics.[90,102]

Novel maintenance approaches to mitigate relapse after allogeneic hematopoietic cell transplantation

The outcomes of younger patients with R/R AML have improved over the years, likely due to advances in therapeutic regimens. In an EBMT registry analysis, Bazarbachi *et al.* showed a significant improvement in OS of younger patients with AML relapsing after allo-HCT in more recent years of transplant (2000-2004; HR=0.82; *P*<0.02 for 2010-2014 and HR=0.72; *P*=0.0002 for 2015-2018).[103] Despite these advances in the treatment of AML and the potential curative approach with allo-HCT in intermediate- and adverse-risk disease, relapse is inevitable in many patients, and they have a dismal prognosis.[104] Post-transplant salvage therapy in AML is an area of unmet need. In relapsed patients, treatments are limited and include palliative care, low-dose or high-intensity treatments, donor lymphocyte infusion, and a second allo-HCT in selected cases. Nevertheless, many patients do not tolerate high-dose therapies, hence the need for novel approaches to prevent or treat relapse. Maintenance strategies have been studied recently in many trials aiming to prevent relapse. The main purpose of post-transplant maintenance is not only to induce a direct anti-leukemic effect through the elimination of any residual leukemia not detected by current laboratory techniques but also to stimulate the GvL effect, ideally without increasing the risk of GvHD.[105] Maintenance therapy can also act as a bridge to mount a GvL effect. Several drugs have been assessed in the post-transplant setting, including a HMA alone or in combination with a *BCL-2* inhibitor or granulocyte colony-stimulating factor, *FLT3* inhibitors, *IDH1/2* inhibitors, and there are early data on histone deacetylase (HDAC) inhibitors; many of these have shown efficacy in the frontline or relapsed setting.

Hypomethylating agent therapy alone or in combination

The HMA azacitidine and decitabine are the most studied drugs in the post-transplant maintenance setting, mainly because of their acceptable safety profile. Data from preclinical animal models have shown that azacitidine, in addition to its direct anti-leukemic effect, can upregulate tumor antigens on leukemic cells, activate CD8$^+$ tumor-specific T cells, and induce regulatory T-cell activity. This in turn increases the GvL effect without a concomitant increase in GvHD.[106] Following these findings, several trials were conducted to investigate the role of these agents as maintenance therapy after allo-HCT.[107] While many studies

support the consideration of a maintenance strategy, some did not demonstrate any benefit.[108]

In a dose-finding phase I trial, the use of azacitidine monotherapy for maintenance was assessed, starting on day +42 after transplantation. Different dose levels were used. The recommended dose for later studies was 32 mg/m^2/day for 5 days in a 30-day cycle. Higher doses were associated with thrombocytopenia. After 12 months of follow-up, the median disease-free survival was 58%, and the 1-year OS was 77%.[109] In another phase I/II trial, azacitidine was administered at a dose of 36 mg/m^2/day for 5 days in a 28-day cycle leading to an increased GvL effect through induction of circulating regulatory T cells without an increase in GvHD.[106] In a case series including 18 patients with AML or MDS who were *FLT3*-negative and in remission following allo-HCT, post-transplant azacitidine maintenance was assessed after starting at a median of 60 days after transplantation. Patients received low-dose azacitidine 32 mg/m^2/day for 5 days in a 28-day cycle for up to 5 years.[110] A phase III trial comparing azacitidine monotherapy maintenance after allo-HCT at a dose of 32 mg/m^2/day for 5 days in a 28-day cycle to no intervention did not show benefit of azacitidine maintenance. Azacitidine was administered for up to 12 cycles (median, 4; range, 1-12). The study included 87 patients with AML, MDS, or chronic myelomonocytic leukemia. After a median follow-up of 4.6 years, azacitidine maintenance did not improve RFS. In a subgroup analysis, patients who received nine or more cycles had an increase in RFS, albeit not statistically significant.[111] Despite the negative azacitidine maintenance phase III trial, the use of maintenance therapy should not be abandoned for several reasons. First, the trial involved patients with high-risk disease, including those with *FLT3* mutations. Studies have shown that patients with *FLT3*-mutated AML benefit from the addition of *FLT3* inhibitors as maintenance therapy, as discussed later in this review.[112] The inclusion of this population could have affected the result of the trial. Second, the study had some selection bias as it excluded patients who received azacitidine for MRD-positive disease. This strategy is denoted as pre-emptive rather than maintenance; those patients might have needed higher doses of azacitidine in addition to other treatment approaches.

Oral azacitidine (CC-486) maintenance improved OS and RFS in older patients with AML in remission after induction therapy in the QUAZAR-AML-001 trial.[113] Based on these results, CC-486 was studied as maintenance therapy in patients in CR after allo-HCT. In a phase I/II trial, CC-486 was given to seven patients at a dose of 200-300 mg for 7 days and to 23 patients at a dose of 150-200 mg for 14 days in up to 12 cycles of 28 days. The 1-year RFS was 54% and 72%, respectively. CC-486 was tolerated, with gastrointestinal and hematologic toxicities being the most common grade 3-4 adverse events. Only two patients developed chronic GvHD.[114] The AMADEUS phase III trial (NCT04173533)

is ongoing and will address concerns regarding dosing, treatment schedule, and therapy duration using maintenance oral azacitidine (CC-486) compared to placebo for AML and MDS in CR after allo-HCT.

Decitabine was also studied for maintenance therapy after allo-HCT. A small dose-finding study assessed the use of low-dose decitabine maintenance therapy after allo-HCT for patients with AML or MDS in CR. Decitabine was given at a dose of 5, 7.5, 10, or 15 mg/m^2/day for 5 days in a 6-week cycle starting between day +50 and day +100. The maximum tolerated dose was not reached but 10 mg/m^2 was chosen because of hematologic toxicities with the 15 mg/m^2 dose.[115] Results showed a high 2-year OS of 56% and a low cumulative incidence of relapse of 28%. This study indicated that decitabine is safe after allo-HCT and could potentially be used as maintenance therapy. A phase II, open-label, multicenter, randomized controlled trial explored the use of decitabine for maintenance in 204 patients with high-risk AML in CR who were MRD negative after allo-HCT. Patients were randomized, between days 60 and 100 after allo-HCT, to receive recombinant human G-CSF in combination for 6 days with low-dose decitabine for 5 days (G-DEC) or no intervention. The cumulative incidence of relapse was lower in the G-DEC group at 15% compared to 38% in the no-intervention group (HR=0.92; 95% CI: 0.18-0.57; *P*<0.1). There was no statistically significant difference in the incidence of chronic GvHD (G-DEC 23% *vs*. no-intervention 21.7%; *P*=0.81).[116] Immune cell subtype monitoring revealed a significant increase in CD8$^+$ and regulatory T cells and NK cells by the second or third cycle in the G-DEC group (*P*<0.5).

The latter results are encouraging and demonstrate a potential benefit of maintenance therapy. Nevertheless, more randomized trials are needed to identify the population of patients who would benefit from maintenance therapy, find the best combination, and standardize the dose and schedule of treatment.[117]

BCL-2 inhibitors

BCL-2 inhibitors, mainly venetoclax, showed promising results in the treatment of AML. Hence, venotoclax was studied in the post-transplant setting. In a cohort study, 23 patients with high-risk AML/MDS in remission after allo-HCT received venetoclax (400 mg daily) for 1 year.[118] Venetoclax was withheld or its dose was reduced in 11 of the 23 patients. The most common adverse events were cytopenia (7/23) and diarrhea (7/23). Six-month OS and RFS rates were both 87%. This was a small cohort study showing the safety of venetoclax after transplantation. However, doses of venetoclax had to be withheld or reduced in many patients, perhaps because of the continuous daily dosing of the drug rather than administration on fixed days per cycle, allowing cell count recovery. An ongoing phase I trial is currently assessing adding venetoclax to fludarabine/busulfan

conditioning and azacitidine maintenance after allo-HCT in patients with AML/MDS (NCT03613532).

The venetoclax and low-dose decitabine combination was assessed in a prospective study to prevent relapse in high-risk patients with AML or MDS.[119] Decitabine was given at a dose of 15 mg/m^2 for 3 days and venetoclax at a dose of 200 mg daily for 21 days starting day +100 after transplantation. Twenty patients were included. No grade ≥3 adverse events were observed. The 2-year OS and EFS were 85.2% and 84.7%, respectively. The 100-day acute and chronic GvHD rates were 55% and 20%, respectively. Furthermore, treatment of GvHD did not affect maintenance therapy.[119] These studies show that the addition of venetoclax to an HMA to prevent relapse is feasible and safe. Randomized trials should be conducted to confirm these findings, establish the best treatment schedule, and identify patients who would benefit from a combination maintenance approach.

FLT3 inhibitors

FLT3 inhibitors have improved the outcomes of patients with *FLT3*-mutated AML when added to frontline chemotherapy, as shown in the RATIFY trial, making them a reasonable option to consider for maintenance after allo-HCT.[2] In 2015, Antar *et al.* reported the efficacy and safety of sorafenib maintenance in five patients with *FLT3*-ITD-mutated AML in remission after allo-HCT.[120] These results were reproduced in another multicenter retrospective study showing high 2-year PFS and OS rates (73% and 80%).[121,122] In an analysis of the EBMT registry, sorafenib post-transplant maintenance was safe and OS was significantly improved compared to no-sorafenib in 28 patients with *FLT3*-mutated AML receiving allo-HCT with *in vivo* T-cell depletion (2-year OS: 82.8% *vs*. 61.5%; *P*=0.007).[123] Two phase II trials assessed the use of *FLT3*-inhibitors as maintenance therapy for *FLT3*-mutated AML after allo-HCT. The SORMAIN phase II trial randomized patients with *FLT3*-ITD-mutated AML to receive sorafenib for 2 years *versus* placebo. A total of 84 patients were included.[112] The 24-month probability of RFS was significantly higher in patients who received sorafenib (85%) than that in the placebo group (53.3%) with a 74% reduction in relapse or death (HR=0.256, 95% CI: 0.10-0.65; *P*=0.002). The estimated 24-month OS was higher in the sorafenib group (90.5%) than in the placebo arm (66.2%) (HR=0.241, 95% CI; 0.08-0.74; log-rank *P*=0.007). At a median follow-up of 55.1 months, median OS had not been reached in either arm (HR=0.52, 95% CI: 0.24-1.11; *P*=0.086). Results were seen across patients with or without *FLT3*-ITD mutations, suggesting an off-target effect of sorafenib in AML. The RADIUS phase II trial assessed the use of midostaurin compared to placebo in 60 patients. The study showed no difference in outcomes, but it was not powered to detect such differences.[124] Most patients in both trials did not receive *FLT3* inhibitors prior to transplantation.

In a large, open-label, randomized, phase III trial, 202 patients with *FLT3*-ITD-mutated AML were randomized to receive sorafenib or placebo as maintenance therapy after allo-HCT.[125] The median time to starting sorafenib was 30 days after allo-HCT. At a median follow-up of 22.3 months, the cumulative incidence of relapse was significantly better in the sorafenib arm than in the placebo arm (HR=0.25, 95% CI: 0.11-0.57; *P*=0.0010). The 2-year leukemia-free survival and OS rates were significantly higher in the sorafenib arm than in the placebo arm: 78.9% *versus* 56.6% (HR=0.37, 95% CI: 0.22-0.63; *P*<0.0001) and 82.1% *versus* 68% (HR=0.48, 95% CI: 0.27-0.86; *P*=0.012), respectively. These studies establish the utility of sorafenib as maintenance therapy for *FLT3*-ITD-mutated AML after allo-HCT. These findings led to the publication of a position statement of the EBMT including worldwide experts endorsing the use of sorafenib as post-allo-HCT maintenance.[126]

Other more selective FLT3 inhibitors are being evaluated in this setting. The BMT-CTN 1506 phase III trial is ongoing and will address the safety and efficacy of gilteritinib compared to placebo for FLT3-ITD-mutated AML as maintenance after allo-HCT (NCT02997202).[127]

IDH1/2 inhibitors

As mentioned earlier, *IDH1/2* inhibitors have proved efficacious as monotherapy or combined with HMA or induction chemotherapy in the frontline and relapsed setting.[4,68] Patients with *IDH*-mutated AML undergoing allo-HCT with MRD-positive disease have a higher risk of relapse.[83] Given the favorable safety profile of ivosidenib and enasidenib, these agents would be suitable for post-transplant maintenance. Several studies are currently evaluating the safety and efficacy of *IDH1/2* inhibitors for *IDH*-mutated AML after allo-HCT (NCT03564821, NCT03515512, NCT03728335, NCT04522895).

Eprenetapopt for *TP53*-mutated acute myeloid leukemia

Allo-HCT is the only curative therapy for patients with *TP53*-mutated AML. However, despite allo-HCT, their outcomes remain very poor. Eprenetapopt, as described above, is a first-in-class clinical-stage molecule reactivating mutant p53.[77]

In a phase II, single-arm, open-label trial, presented at the Tandem meetings in 2022, eprenetapopt was given at a dose of 3.7 g/day for 4 days in combination with azacitidine at a dose of 36 mg/m²/day for 5 days.[128] Thirty-three adult patients with *TP53*-mutated AML (n=14) or MDS (n=19) were included. Ten out of 14 patients with AML had detectable *TP53* at the time of their transplant. Grade 3-4 adverse events were mainly hematologic. The 1-year RFS was 58%. With a median follow-up of 429 days, the median OS was 586 days, and the 1-year OS was 79%. No apparent treatment-related increase in GvHD was observed. Acute and chronic GvHD were documented in four and ten patients,

respectively. These results show that eprenetapopt maintenance after allo-HCT is safe and certainly promising and its use should be studied further in a large, randomized, phase III trial.

Histone deacetylase inhibitors

HDAC inhibitors are epigenetic modifiers that have direct anti-leukemic and immunomodulatory activity. Additionally, they can modulate regulatory T-cell activity.[129] Panobinostat is an oral pan-HDAC inhibitor that has a much higher affinity to class I than to class II HDAC. At a low dose, it saturates class I receptors leading to decreased regulatory T-cell inhibitory function. At higher doses, it saturates class I receptors and attaches to class II receptors which become dominant. This leads to increased regulatory T-cell activity. These properties make it a theoretically suitable drug for post-allo-HCT maintenance.[129] The phase I/II PANOBEST trial assessed the feasibility of panobinostat in patients with high-risk AML or MDS in CR after allo-HCT. Patients were treated on a weekly or every other week schedule. Dose-limiting toxicities were reached at 20 mg and 30 mg in the weekly and every other week schedules, respectively. In the phase II part of the trial, patients were randomized to one or other of the schedules using the dose-limiting toxicity identified. The median time of starting panobinostat was 96 days. The main grade 3-4 adverse event was thrombocytopenia (weekly schedule: 28%, every other week: 19%). The cumulative incidence of chronic GvHD at 2 years was 29% and did not differ between the two schedules.[130] The 2-year OS and RFS were 81% and 75%, respectively. The findings of this trial are promising, and results are being confirmed in the large phase III ETAL-4/HOVON-145 trial (NCT04326764).

Immunotherapy

Other agents are being investigated with the aim of preventing relapse after allo-HCT. Monalizumab, an IgG4 monoclonal antibody, is an NKG2A checkpoint inhibitor. It improves the NK cell-mediated GvL effect without increasing the risk of GvHD.[131] In a phase I dose-finding study presented at the American Society of Hematology meeting in 2021, monalizumab was given at a median time of 83 days after allo-HCT to 15 patients with a hematologic malignancy, including nine with AML and three with MDS. No dose-limiting toxicities were observed, justifying the use of the 1 mg/kg dose. No disease recurrence was observed in patients with AML. Future studies should aim at assessing the efficacy of monalizumab in the clinical setting.[132]

Conclusions and perspective

Targeted therapy has revolutionized the treatment of AML and improved outcomes. However, in the frontline setting

standard induction chemotherapy for fit patients and low-intensity treatment (HMA, LDAC) for unfit patients remain the backbone to which targeted therapies are added. Venetoclax is used in the frontline and in the relapsed setting in combination with chemotherapy or HMA owing to its synergistic effect, broadening treatment options, particularly for patients without identified targetable mutations. With the advent of next-generation sequencing, several mutations have been discovered; and future studies should aim at deciphering their role in the pathogenesis of AML. There is also an unmet need to develop novel approaches to target or bypass these mutations.

Up to now, allo-HCT has been the mainstay treatment for patients with intermediate- and adverse-risk AML in remission after frontline therapy. We believe that future work should focus on assessing the role of allo-HCT in the era of novel therapies, particularly in the intermediate risk group. With the introduction of next-generation sequencing, the prognostic value of MRD before and after allo-HCT needs to be evaluated. Early studies show worse outcomes after allo-HCT in patients with persistent MRD detectable by next-generation sequencing.[83,133] Conditioning regimens have not changed markedly over the last few years despite the emergence of new conventional chemotherapies with anti-leukemia activity. Adding targeted therapies to conventional conditioning regimens (MAC or RIC), is being studied but long-term follow-up is still needed to better understand the effect of the combinations on engraftment as well as early and late post-transplant complications and GvHD. Allo-HCT alone has proven to provide long-lasting remissions, although relapses still occur in many patients. Prospective studies should aim to identify patients in need of therapies, whether as maintenance or post-transplant consolidation, to prevent relapse. As with *FLT3*-mutated AML, in which sorafenib is an established, effective maintenance strategy,[126] studies should focus on assessing the role of post-allo-HCT maintenance in other groups of AML. Furthemore, the optimal duration of post-allo-HCT maintenance therapy is not well established, with most studies using an arbitrary duration of 1 to 2 years. However, in the real-life setting, the decision to discontinue maintenance in patients tolerating such therapies is certainly challenging. Accordingly, studies are needed to help to define the optimal maintenance regimen and identify patients who are most likely to benefit.

Disclosures

No conflicts of interest to disclose.

Contributions

RM designed and wrote the manuscript. RAH wrote the manuscript. EB, AB, and MM supervised the work and helped to write the manuscript. All authors reviewed and agreed on the final version of the manuscript.

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