REVIEW ARTICLE

Maintenance therapy in acute myeloid leukemia: advances and controversies

Jayastu Senapati, Tapan M. Kadia and Farhad Ravandi

Department of Leukemia, The University of Texas, MD Anderson Cancer Center, Houston, TX, USA

Correspondence: F. Ravandi
fravandi@mdanderson.org

Received: January 31, 2023.
Accepted: April 24, 2023.
Early view: May 4, 2023.

https://doi.org/10.3324/haematol.2022.281810

Abstract

The last decade has seen steadfast progress in drug development in acute myeloid leukemia (AML) which has moved progressively towards genomic-based therapy. With these advances, outcomes in AML have improved but remains far from satisfactory. One approach towards preventing relapse in AML is to use maintenance therapy in patients, after attaining remission. Allogeneic hematopoietic stem cell transplantation (HSCT) is an effective post-remission therapy that has been proven to reduce the risk of relapse. However, in patients who are ineligible for HSCT or have a high risk of relapse, other effective measures to prevent relapse are needed. There is also a need for post-HSCT maintenance to reduce relapse in high-risk subsets. Over the last 3 decades maintenance therapy in AML has evolved from the use of chemotherapeutic agents to more targeted therapies and better modulation of the immune system. Unfortunately, improvements in survival outcomes as a result of using these agents have not been consistently demonstrated in clinical trials. To derive the optimum benefit from maintenance therapy the time points of therapy initiation need to be defined and therapy must be selected precisely with respect to the AML genetics and risk stratification, prior treatment exposure, transplant eligibility, expected toxicity and the patient's clinical profile and desires. The far-reaching goal is to facilitate patients with AML in remission to achieve a normal quality of life while improving remission duration and overall survival. The QUAZAR trial was a welcome step towards a safe maintenance drug that is easy to administer and showed survival benefit but leaves many open issues for discussion. In this review we will discuss these issues, highlighting the development of AML maintenance therapies over the last 3 decades.

Introduction

The recent evolution of targeted therapeutics in acute myeloid leukemia (AML) along with better understanding of disease biology and deeper assessment of post-treatment measurable residual disease (MRD) have improved outcomes of patients with this disease.[1] However, despite the attainment of deep remission in AML, i.e. a MRD-negative state, a majority of patients with non-acute promyelocytic leukemia AML relapse over time, with approximately 40% of MRD-negative patients relapsing within 5 years.[2-4] Thus, in the absence of ongoing therapy or active immune surveillance, despite attaining significant disease control, patients with AML are prone to relapse. Traditionally, allogeneic hematopoietic stem-cell transplantation (HSCT) has been the default approach to potentiate immune surveillance in AML through a graft-*versus*-leukemia effect. In transplant-eligible patients with adverse-risk and intermediate-risk AML, HSCT has led to improved disease-free survival (DFS).[5] However not all patients are eligible for HSCT, and even for those transplanted, relapses occur and remain challenging to treat. An alternative option for controlling the undetectable yet residual burden of leukemic cells could be through maintenance therapy.

Maintenance therapy, or administration of a less intensive, prolonged therapy after initial intensive induction-consolidation (I-C) chemotherapy has been the standard of care in acute lymphoblastic leukemia[6] and acute promyelocytic leukemia.[7] Multiple studies have explored the utility of this approach in patients with AML, and with the recent approval of an agent for the first time in this setting, the field is continuing to evolve. With further refinement of maintenance therapy concepts, including the appropriate settings and timing of maintenance therapy, the development of well-tolerated and effective agents and/or combinations and better definition of the endpoints such

as MRD eradication, we are likely to witness more interest in incorporating maintenance strategies into treating patients with AML. The phase III QUAZAR trial comparing CC486 (an oral formulation of azacitidine not bioequivalent to the parenteral form) to placebo in adult patients (≥ 55 years) with AML in remission and not candidates for immediate HSCT, demonstrated a significantly improved overall survival (OS) in the treatment arm, leading to the approval of the drug in this setting.[8] However, despite the initial advantage for median survival in the treatment arm, with further follow-up, the desired plateau of sustained OS and relapse-free survival (RFS) was not achieved.[9] Several questions do, therefore, remain unanswered, primary among which are eliciting the true benefit of maintenance strategy in patients who complete all planned courses of I-C therapy, have MRD-negative remission and the impact of subsequent salvage therapies.[10] In this review we discuss the advances and controversies surrounding maintenance therapy in AML by exploring its need, available results from clinical trials over the last 3 decades and implications in modern AML therapy.

How do we define a maintenance therapy?

With progressive refinement of AML therapy, it is important that maintenance therapy be defined with respect to its intensity, timepoint of use in the treatment schema, and status of disease control. Conventionally, maintenance therapy has been denoted as low-intensity therapy given over a relatively long duration after attainment of at least morphological disease control.

Over the past several years, treatment strategies, particularly in older patients with AML, have progressively evolved to several effective, low-intensity regimens.[11-13] As data with these approaches are gaining traction, they will likely be evaluated in relatively younger patients for remission induction and consolidation. Thus, therapy intensity alone cannot be used to define a maintenance regimen. In patients who receive recurrent cycles of a low-intensity regimen, the same regimen is usually continued after attaining remission, frequently at progressively reduced doses, until disease progression or toxicity. At what point are these treatment cycles considered to transition from 'consolidation' to 'maintenance' while using the same drugs? Historically maintenance therapy trials in AML included agents that were different from those used for the initial AML therapy, which were commonly conventional chemotherapeutic agents. Thus, the differentiation was clear. Recent trials and maintenance concepts, especially with low-intensity therapy in AML, often use the same regimens in attenuated doses, which make this differentiation less distinct.

As assessment of MRD in AML has become commonplace, do we consider maintenance therapy as treatment received after attainment of MRD-negative remission or in the setting of persistent MRD – so-called 'MRD eradication'? However, with increasingly effective intensive and non-intensive regimens, pre-maintenance consolidation treatment after remission induction is very often preceded by an MRD-negative state. Thus, therapy following an MRD-negative state cannot be universally deemed to be a maintenance regimen. The European LeukemiaNet 2021 consensus statement recommends that assessment of MRD (in the bone marrow) be ideally done after consolidation therapy and cutoffs for different assays (flow cytometry or molecular methods using polymerase chain reaction or next-generation sequencing) for both MRD negativity and MRD relapse have also been defined.[14] Such harmonization of MRD timepoints is important in order to choose subsequent treatment strategies; however, most of these recommendations are geared towards the need for consolidative HSCT while the use of maintenance therapy for MRD eradication in patients with persistent low-level MRD or MRD recurrence remains an unresolved issue. The concept of maintenance therapy in patients in MRD-positive remission could possibly include MRD eradication or 'conversion' from an MRD-positive to negative state.

Hence, in the absence of defined timepoints for maintenance therapy initiation, as used in clinical trials, the definition of maintenance therapy in clinical practice is variable, often contextual and physician-derived. It depends largely on the baseline AML genomics, the depth of remission attained and the possibility of proceeding to a subsequent HSCT. Better definition of these time points is important for improved understanding of the true benefit of maintenance therapy in clinical trials as well as in retrospective data curation. Possible considerations towards this are:

- In the context of intensive therapy, maintenance therapy may include therapy that is administered as a repetitive, low-intensity treatment after consolidation therapy and with undetectable/stable low-level MRD (e.g., decitabine maintenance after fludarabine, cytarabine, granulocyte colony-stimulating factor-based therapy in core-binding factor [CBF] AML)
- For low-intensity remission induction approaches, maintenance therapy may include therapy administered after attainment of an MRD-negative state or with stable low-level MRD with at least 50% dose (dose/duration) reduction of the drugs from the initial therapy, if the same agents are used, or at any dose if the therapy is altered/reduced to a more targeted regimen (e.g., reduced dose azacitidine-venetoclax maintenance after azacitidine-venetoclax induction; gilteritinib maintenance after azacitidine-venetoclax-gilteritinib induction)
- Therapy initiated after HSCT irrespective of MRD status (e.g., sorafenib or azacitidine maintenance after HSCT)

The need for maintenance therapy in acute myeloid leukemia

All patients with AML are prone to relapse. Although it is now possible, using more sophisticated assays, to test for the achievement of deeper responses, deleterious residual disease below the level of detection (Figure 1), often at the leukemic stem cell level, fuels disease relapse.

The aim of maintenance therapy is to prevent clonal evolution and growth while the immune system is able to overcome the burden of residual leukemia cells. In the era of conventional chemotherapy, further intensification in I-C cycles often failed to show any linear improvement in survival.[15-18] HSCT was associated with better long-term survival after such intensive therapy in patients with non-favorable-risk AML. Most maintenance trials from this period failed to show any improvement in OS and often fell short of demonstrating benefit in relapse-/leukemia-/disease-free survival. This is likely due to the lack of availability of highly effective, well-tolerated agents with different mechanisms of action compared to standard cytotoxic chemotherapy.

Through rational combination regimens with the addition of novel drugs, such as venetoclax, we are now able to achieve both higher response rates and deeper responses. Could the true benefit of maintenance therapy be evident at this depth of response? Results from the UK NCRI AML 16 trial showed that in older patients with AML (>60 years) in complete remission (CR) after intensive chemotherapy, maintenance with azacitidine led to improvement in 5-

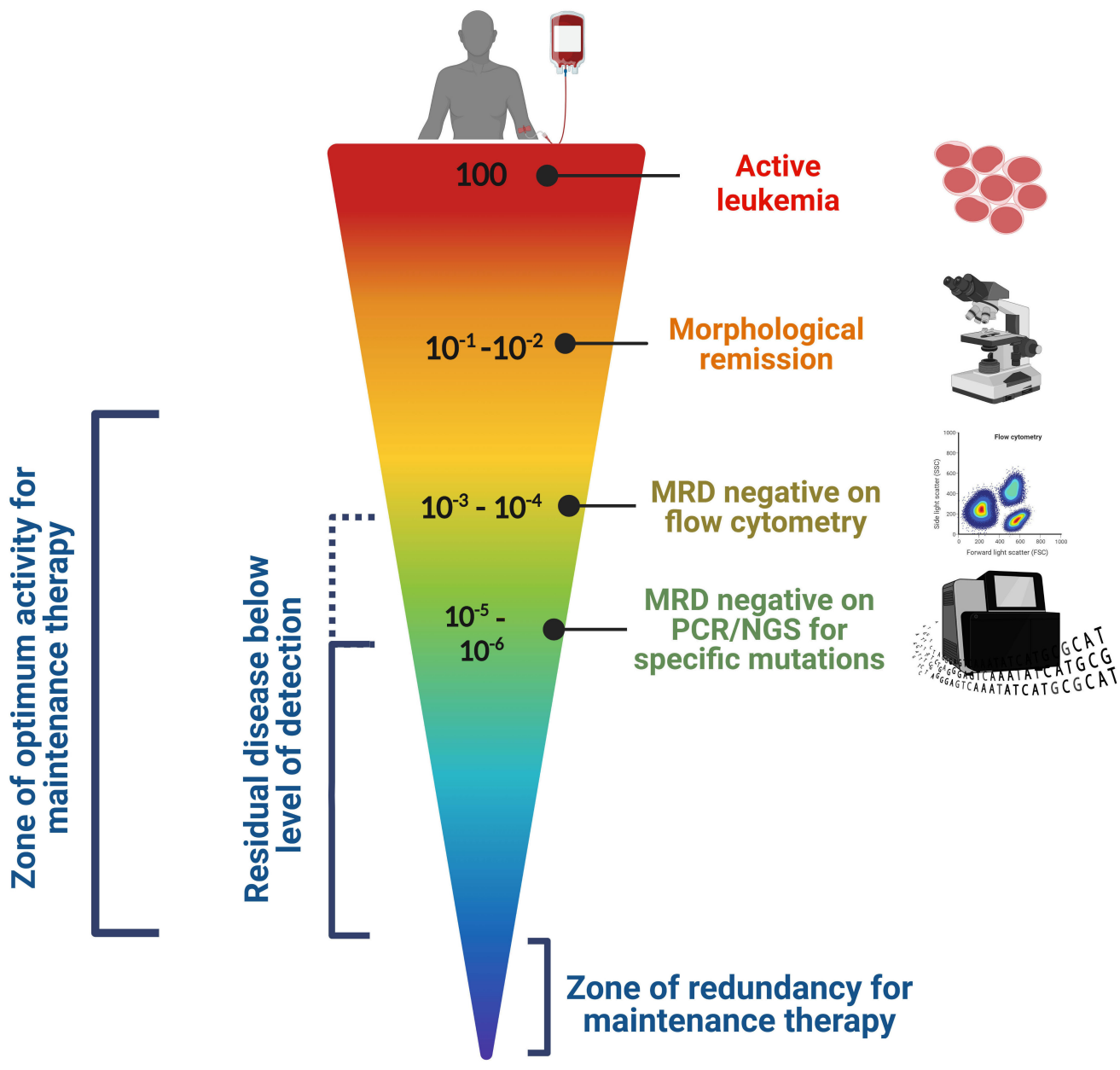

Figure 1. Finding the biological niche for maintenance therapy in acute myeloid leukemia. Finding the right depth of disease control for initiating maintenance therapy in acute myeloid leukemia (AML) is important to garner the greatest benefit from this approach. In patients with significant measurable residual disease (MRD), maintenance therapy might not lead to durable morphological relapse-free survival. The exact cutoff of this MRD is not known but would largely vary based on the AML genomics and type of maintenance therapy used. In patients with very low disease burden, often below the level of detection by modern MRD assays and thus not quantifiable, the use of maintenance therapy might not lead to significant benefit but add to toxicity. In high-risk AML, deep remissions are often difficult with therapy, and short of a hematopoietic stem cell transplantation, maintenance therapy with low-level stable MRD can still be beneficial to improve morphological relapse-free survival. Dynamic monitoring of MRD to guide the duration and intensity of maintenance therapy in conjunction with the extent of toxicity is relevant in clinical practice. MRD: measurable residual disease; PCR: polymerase chain reaction; NGS: next-generation sequencing. Figure made on BioRender.com

year OS only in those who were MRD-negative at 10^{-4} (40% *vs*. 13%) but not in those who were MRD-positive (20% *vs*. 23%).[19] In the randomized HOVON97 trial comparing azacitidine maintenance to observation in older patients (≥60 years) with newly diagnosed AML after intensive chemotherapy, 12-month DFS was superior in the therapy arm than in the observation arm (64% *vs*. 42%), however on a multivariate time-to-event regression analysis using baseline disease risk, CR or CR with incomplete count (CRi) recovery etc. as variables, only the presence of a platelet count ≥100x10^9/L (equated to CR) at initiation of maintenance therapy stood out as a significant factor for improved DFS.[20] Although MRD data were not available from this trial, CR could reflect a superior disease control state over that indicated by CRi; this again highlights that the real benefit of maintenance therapy with parenteral azacitidine may be accrued in those who have prior better disease control. In the landmark QUAZAR trial, patients in the treatment (CC-486) arm showed a statistically significant improvement in OS (24.7 *vs*. 14.8 months) in the whole population.[8] However, in an exploratory analysis, the 2-year OS benefit of CC-486 over observation was significant in the MRD-positive subgroups rather than in the negative group, although again the improvement was more significant for patients in CR than CRi. Randomized trials stratifying patients based on their disease status at the time of AML maintenance, genomics and prior therapy exposure are needed to understand the population in which maintenance therapy is expected to work best.

Lastly, whether maintenance therapy reduces the effectiveness of salvage at relapse is unknown and might possibly depend on the type of regimens used. If so, improving first remission duration with maintenance therapy might not lead to an OS benefit (Figure 2). This needs to be explored through clinical trials by assessing the response to salvage regimens in patients who relapse after a significant duration of maintenance therapy.

An ideal maintenance regimen

Though an ideal maintenance regimen should suppress the evolution of the relapse-prone residual leukemic cells, this should not lead to additional therapy-related genomic instability. Secondly, the regimen should not lead to a significant additional toxicity burden to the patient through an increased risk of infections, need for recurrent transfusions and overall poor quality of life. This is supremely important because these regimens are being advocated in patients who are already in remission (often with good blood counts). Despite the general safety of hypomethylating agents (HMA) as maintenance therapy, these drugs can still cause cytopenia, which can increase risks of infection and need for transfusions, especially when they are combined with agents such as venetoclax. When used as maintenance therapy after HSCT, immunomodulatory drugs such as lenalidomide have been shown to increase risks of graft-*versus*-host disease (GvHD), significantly, while immune checkpoint inhibitors can also lead to immune toxicities such as autoimmune hepatitis and colitis. Thirdly, the regimen should be easy to administer and require less frequent monitoring and hospital visits. In reference to

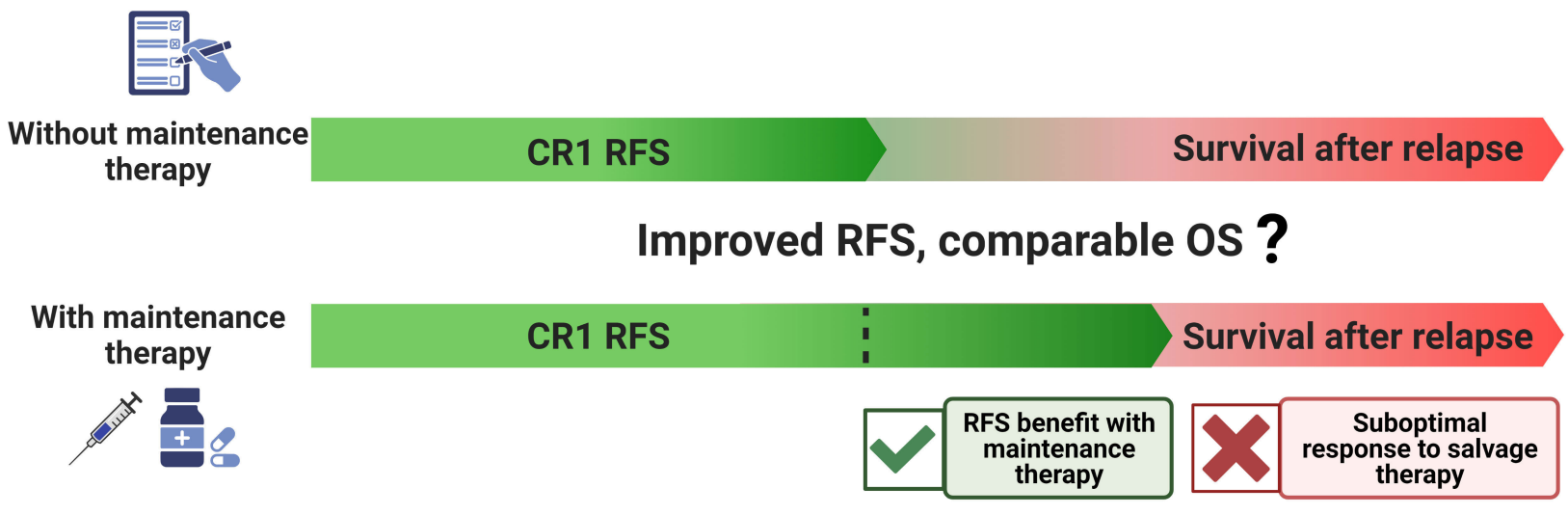

Figure 2. Impact of maintenance therapy on survival in acute myeloid leukemia. Several clinical trials with maintenance therapy in acute myeloid leukemia (AML) have shown benefits in relapse-free survival (RFS), but overall survival (OS) benefits have been reported exceedingly rarely. Maintenance therapy by virtue of suppressing the residual disease clone can improve the duration of morphological RFS. However, the effectiveness of salvage regimens in post-maintenance therapy relapse settings needs to be studied. Prolonged exposure to maintenance regimens in some patients can make the AML more resistant through increased subclonal heterogeneity under therapy pressure, especially if the maintenance therapy is not able to diminish the residual leukemia clones to significant depths. This might make the likelihood of response to subsequent salvage therapy low. Thus, OS might not increase proportionally to RFS with maintenance therapy. In randomized clinical trials with maintenance therapy, response to salvage therapy and survival outcomes of patients after relapse in both maintenance therapy arms, and observation arms should be detailed for better understanding of these dynamics. CR1: first complete remission; RFS: relapse-free survival; OS: overall survival. Figure made on BioRender.com

maintenance regimens advocated after HSCT, they should not increase risks of GvHD, counter the important graft-*versus*-leukemia effect, cause graft suppression, or interfere with post-transplant immunosuppressive medications.

Although monotherapy against targetable mutations (especially if they are persistent at the time of starting maintenance therapy) would appear as the most suitable option (e.g., FLT3/IDH inhibitors), they can fuel the risk of clonal escape and relapse under treatment pressure. Considering the subclonal heterogeneity of AML, combinations such as HMA plus venetoclax or other targeted agents may be better maintenance options given their broader mechanism of action. There are no available comparative data, but it will be important to evaluate and compare the potency and toxicity of these regimens as maintenance therapy. The choice could be made easier in patients without targetable mutations or in those in whom the mutations by themselves are known to drive relapse (e.g., *FLT3*-ITD).

The evolution of maintenance therapy in acute myeloid leukemia

The clinical development of maintenance therapy in AML has traversed from harnessing the immune system through the use of interleukins, interferon (and donor lymphocyte infusion in the post-HSCT setting), immunomodulatory agents such as lenalidomide to low-intensity chemotherapy, HMA, and now to the present use of targeted therapies or adoptive cellular therapy (Table 1).

Non-allogeneic stem cell transplanted-directed maintenance

Chemotherapy

The earliest studies of maintenance therapy in AML used low-intensity chemotherapy in different combinations after intensive I-C regimens, without much success. In 1984, Sauter and colleagues were the first to report on the lack of efficacy of adding relatively low doses of cytarabine (100 mg/m^2 for 5 days per cycle repeated every 8 weeks) to 6-thioguanine alternating with prednisone and vincristine for 2 years in patients in remission after intensive chemotherapy (*vs*. observation). Both groups had a median remission period of 18 months and survival of 30 months.[21] Shortly after, the German AML Cooperative Group published the results of their frontline AML study (2 clinical trials) showing improved continuous remission duration but not OS in the cohort randomized to maintenance (alternating low-dose cytarabine + daunorubicin, low-dose cytarabine + 6-thioguanine, and low-dose cytarabine + cyclophosphamide) over observation after intensive chemotherapy.[22] The Eastern Cooperative Oncology Group study, in which patients with AML in second relapse or later, or with refractory disease and attaining remission with intensive salvage chemotherapy were randomized to treatment with low-dose cytarabine (10 mg/m^2 twice a day for 21 days each cycle repeated every 2 months until disease relapse) or observation showed that patients in the therapy arm had statistically improved DFS (7.7 *vs*. 3.3 months) but not OS.[23]

A few other trials also using a chemotherapy-based maintenance approach failed to show any meaningful improvement in survival outcomes. The Southwest Leukemia Group, in a small study, failed to show improvements in RFS and OS with 6-thioguanine, etoposide and CCNU-based maintenance.[24] The EORTC-HOVON trial showed an improvement in DFS but not OS with low-dose cytarabine maintenance compared to observation at remission after intensive therapy but the actual figures were still dismal (4-year DFS: 13% *vs*. 7%).[25] In the LAME 89/91 study of pediatric patients with AML, DFS was similar in the maintenance (18 months of monthly low-dose cytarabine 25 mg/m^2 twice a day for 4 days and continuous 6-methylprednisone) and observation groups while OS was inferior in the maintenance arm.[26] Given the long-term poor OS (with or without maintenance therapy) with such chemotherapy-based approaches in non-HSCT patients from an era without MRD assessment in AML, the applicability of these data to modern day AML therapy is low and thus chemotherapy-based maintenance in AML is not routinely practised.

Immune adjuvants

HSCT led to improvements in RFS and OS in patients with AML transplanted in remission, underpinning the importance of potent immune surveillance in preventing relapse. Interleukin-2 was the forerunner in this aspect with several studies looking into its potential utility as a maintenance agent. Biologically, interleukin-2 is a potent activator of cytotoxic T cells and natural killer cells;[27-33] however, multiple well-designed clinical trials from the late 1990s to 2010 failed to show a benefit in leukemia-free survival (LFS) or OS with interleukin-2 as maintenance therapy in children, adults or older patients with AML.[34-39] The last in this series was the relatively recently published report of the ELAM02 randomized controlled trial in childhood AML in which patients in remission and not undergoing HSCT after intensive I-C therapy were randomized to receive interleukin-2 or remain under observation; there was no improvement in DFS or OS with the use of interleukin-2.[40] Two separate meta-analyses showed the futility of interleukin maintenance over observation on DFS and OS; one was an analysis of patient-level data from adults with AML in five randomized controlled trials (905 patients)[41] while the other analysis concerned 1,426 pediatric and adult patients.[42]

Table 1. The different maintenance therapy approaches, and their clinical utility based on the MD Anderson experience.

	Chemotherapy	IL2±HDC	Lenalidomide	Hypomethylating agent				Targeted therapy		DLI
				Monotherapy	Lenalidomide	Nivolumab	Venetoclax	FLT3 inhibitors*	IDH inhibitors	
Efficacy	+	++	+	+++	++	++	+++	+++	+	++
Toxicity	+++	++	+++	++	+++	+++	++	+	+	++
Ease of administration	-	-	+++	++ Oral: +++	+	-	+	+++	+++	+
Precision-based	-	-	-	-	-	+	+	+++	+++	-
Available data	+++	++++	++	++++	++	++	++	+++	+	++
RCT	Y	Y	N	Y	N	Y	N	Y	N	N
Meta-analysis	N	Y	N	Y	N	N	N	N	N	N
Overall relevance	-	-	-	+++	+	+	++	+++	+++	++
Benefit in special settings			High-risk AML	No targetable mutation, CBF-AML, Post-HSCT		Post-HSCT	High-risk AML, No targetable mutations, *NPM1*^{mut} AML	*FLT3*^{mut} AML, Sorafenib post-HSCT	*IDH*^{mut} AML, post-HSCT	Only post-HSCT

The table shows the clinical utility (safety, efficacy, ease of administration) of the commonly used approaches in acute myeloid leukemia maintenance and summarizes their current relevance considering the available data. The respective rows are graded from absent/poor (-) to high/good (++++). This scoring is a rough estimate based on available data and our institution's practice and experience. *Among FLT3 inhibitors, sorafenib and midostaurin have been specifically studied from the aspect of maintenance therapy and both in the post-transplant setting (SORMAIN and RADIUS trial, respectively). A phase III randomized controlled trial with gilteritinib in the maintenance setting is underway, while other trials of midostaurin (RATIFY), gilteritinib (ADMIRAL) and quizartinib (Quantum R and QuANTUM First) did not specifically study the drug in the maintenance setting. IL2: interleukin 2; HDC: histamine dihydrochloride; *FLT3*: FMS-like tyrosine kinase 3; *IDH*: isocitrate dehydrogenase; DLI: donor lymphocyte infusion; RCT: randomized controlled trial; Y: yes; N: no; CBF-AML: core-binding factor acute myeloid leukemia; HSCT: hematopoietic stem cell transplantation; *NPM1*: nucleophosmin 1.

To develop this concept further, histamine di-hydrochloride was added to interleukin-2, in an attempt to reduce the paracrine effect of leukemic cell-derived reactive oxygen species (through the action of the histamine di-hydrochloride on leukemic cells),[43] which inhibit the activity of T and natural killer cells.[44,45] In the first large trial, reported by Brune and colleagues, comparing this combination as a maintenance regimen to observation in 320 adult patients with AML, interleukin-2 + histamine di-hydrochloride was associated with improved LFS (2-year LFS: 41% *vs*. 29%) but no difference in OS (leading to European Medicines Agency approval of this combination for maintenance in AML).[46] Further mature data with this combination as a maintenance regimen in AML are lacking. Not surprisingly, Interferon-α has also been studied as a maintenance drug in AML; two randomized clinical trials, one from Finland by Palva and colleagues and the other from the UK (MRC AML11 trial), failed to show a beneficial effect of interferon-α maintenance on DFS or OS.[47] In a more recent report from China, the use of interferon-α maintenance for 12-18 months led to improved 4-year RFS (87% *vs*. 56%) and OS (94% *vs*. 76%) when compared to a retrospective cohort who had received similar I-C therapy but no interferon-α maintenance.[48] Interferon-α is not, however, a well-tolerated drug and has not been further investigated in this setting.

Lenalidomide is a potent immunomodulatory drug and is a widely established maintenance agent in multiple myeloma.[49] A single-arm study from the MD Anderson Cancer Center (MDACC), studied lenalidomide maintenance for up to 24 months in patients with high-risk AML in first or subsequent CR and not eligible for HSCT.[50] Over a third of patients were able to complete all 24 cycles and the 2-year RFS and OS were 50% and 63%. Of note, 25% of patients had an adverse-risk mutational profile, 21% had adverse cytogenetics and 54% had MRD at the time of starting lenalidomide. In a study by the HOVON-SAKK group lenalidomide as maintenance did not improve RFS; however, the initial therapy was variable including some patients who had received an autologous SCT and the numbers of patients at the time of randomization to maintenance *versus* observation were small.[51] In a small, phase I study of 16 patients, six cycles of maintenance lenalidomide, given for 21 days of each of the 28-day cycles, started 6-10 months after HSCT for high-risk myelodysplastic syndrome (MDS) or AML, resulted in a 2-year RFS of 80%; seven patients developed GvHD (dose-limiting in 2 cases).[52] The LENAMAINT trial (NCT00720850) that was designed to test lenalidomide as maintenance therapy after HSCT in patients with del5q or monosomy 5 AML/MDS was terminated due to slow recruitment and possible increased GvHD. Thus, unlike in multiple myeloma, lenalidomide has failed to be a prominent maintenance agent in AML. However, in view of the initial promising data as a single agent, revisiting lenalidomide in combinations or other strategies may be considered.

In the realm of immune activation, immune checkpoint inhibitors have shown promising results in Hodgkin lymphoma,[53,54] Richter syndrome[55] and in several non-hematologic malignancies.[56,57] Immune checkpoint inhibitors, by blocking PD1, PDL1, and CTLA4 (the immune checkpoints), are able to reverse immune cell exhaustion in malignancy and lead to death of cancer cells.[58]

In a single-arm phase II study of nivolumab maintenance in patients with high-risk AML in CR/CRi not eligible for HSCT, 15 patients were treated with nivolumab at a dose of 3 mg/kg every 2 weeks (every 4 weeks after cycle 6 and every 3 months after cycle 12) until disease relapse.[59] At a median follow-up of 30 months, the median RFS was 8.5 months and the median OS had not been reached. In the recent update of the REMAIN trial, nivolumab (3 mg/kg IV every 2 weeks for 46 doses), when compared to observation in 79 patients with AML not eligible for HSCT, did not lead to improved RFS (2-year RFS 30% in both arms) or OS (2-year OS 60% *vs*. 53%), but caused a significantly higher burden of adverse events.[60]

Significant post-HSCT immune toxicities have been reported in patients who have proceeded to transplant after nivolumab maintenance/therapy for AML.[61,62] In the front-line trial of nivolumab added to high-dose cytarabine and idarubicin in 44 patients with AML, serious acute GvHD was seen in 5/19 patients who proceeded to HSCT.[63]

Despite significant insights into harnessing the immune system to treat and maintain remission in cancer, apart from HSCT, immune-based therapy has been largely disappointing in AML. Better understanding of the immune milieu, and further insights into immune function, for example through quantification of PD1-expressing cells in the bone marrow,[63] might help to identify patients who could benefit from an immune checkpoint inhibitor approach. Recent data have shown quite conclusively that a higher ratio of baseline T cells to myeloid leukemia cells is fundamental for subsequent response to immune checkpoint inhibitor-based therapy.[64] Thus, adequate clearance of leukemic cells before administering immune checkpoint inhibitors is essential for improving the activity of these inhibitors as a maintenance therapy. Furthermore, unlike the situation in solid organ malignancies, in which the PD1/PDL1 axis is more pertinent, immune cell exhaustion in AML could be mediated through upregulation of other proteins such as TIM3 on CD4 and CD8 T cells and CD47 on AML cells (preventing macrophage activity), which are being actively studied as therapeutic targets in AML.[65,66]

Epigenetic modifiers: hypomethylating agents

HMA (azacitidine and decitabine) alone or in combination with other agents have been the cornerstone of modern

maintenance strategies in AML. The safety and tolerability of HMA, as well as the wide experience of physicians with them, have made them well suited as potential agents for maintenance in AML.

The first in the series of randomized controlled trials with HMA maintenance was reported by the MDACC in 2012. Decitabine at a dose of 20 mg/m^2 for 5 days every 4-8 weeks for 12 cycles (n=20) was compared to observation (n=6)/low-dose cytarabine (n=9)/intensive chemotherapy (n=10) in adult patients with AML in remission; at a median follow-up of 45 months, no difference in event-free survival (EFS) (32% *vs*. 35%) or OS (36% *vs*. 45%) was found between the two groups.[67] The single-arm CALGB 10503 study using decitabine maintenance in patients <60 years who were in first CR but were not proceeding to HSCT did not show any improvement in EFS or OS compared to their historical controls.[68]

The UK NCRI reported on the data of their AML16 trial in 2015 (described earlier) and for the first time showed an OS benefit with HMA in an exploratory cohort of MRD-negative patients randomized to the azacitidine maintenance arm (75 mg/m^2/day for 5 days every 6 weeks for 9 cycles) compared to observation (5-year OS: 40% *vs*. 13%), but not in the whole cohort (5-year OS *vs*. 24% *vs*. 20%).[19] In 2019, the HOVON group reported the findings of another phase III randomized controlled trial of azacitidine (50 mg/m^2 for 5 days, every 4 weeks for a maximum of 12 cycles) compared to observation in 112 patients ≥60 years with AML/MDS-excess blasts in CR/CRi after intensive therapy. The study showed that DFS was significantly improved in the therapy arm (12-month DFS: 64% *vs*. 42%; *P*=0.04) with no difference in OS (12-month OS: 84% *vs*. 70%; *P*=0.69).[20] The ECOG-ACRIN E2906 study randomized 120 patients ≥60 years with AML in remission to decitabine (20 mg/m^2 for 3 days each 4-week cycle for 1 year) or observation after intensive therapy. At a median follow-up of 50 months after the start of induction therapy, patients in the decitabine arm had better DFS (15.3 *vs*. 8.2 months; *P*=0.12) and OS (25.8 *vs*. 19.5 months; *P*=0.06) but the difference failed to reach statistical significance; notably, in the subgroup of patients with *FLT3*-ITD-negative disease (88% of tested patients, n=84/96), the median OS was significantly better in the decitabine arm (38.2 *vs*. 25.2 months; *P*=0.039).[69] Importantly, in all the above studies HMA maintenance was well-tolerated.

Possibly, the most important trial with HMA maintenance is the QUAZAR AML-001 trial.[8] Administration of CC-486 at a dose of 300 mg/day for 14 days every 28-day cycle until progression produced an improvement in OS compared to that achieved with observation (24.7 *vs*. 14.8 months) at around 12 months of follow-up. However, some issues arose from analysis of the trial: (i) site-wise data assessment showed that the benefit was insignificant in North American study sites compared to European ones; (ii) patients who had received consolidation therapy had statistically inferior reduction in hazards of death compared to those who did not receive any consolidation; (iii) the majority of the patients (68%) had received no or only one cycle of consolidation therapy prior to CC-486 maintenance therapy; (iv) the study included a small proportion of patients with active disease who are not poised to benefit from a maintenance therapy approach; and (v) the duration of maintenance therapy was not defined and some patients with morphological progression on trial had a dose increment of the drug. Nonetheless, the trial did show a statistically significant improvement in OS in the overall population with CC-486 maintenance, which had not occurred in the majority of prior maintenance studies with other agents.

Despite the relatively favorable outcomes in CBF-AML, long-term LFS still remains at 50-60%.[70] However, through precise disease-specific quantitative polymerase chain reaction transcript-based MRD assessment, pre-emptive therapy can be given to prevent morphological relapse.[71] In the CALGB 10503 trial described above, a sizeable percentage of patients (34%) had CBF-AML, and even in them, non-MRD-directed decitabine maintenance did not seem to improve DFS or OS.[68] In a single-arm study from the MDACC of 31 patients with CBF-AML treated with fludarabine-high-dose cytarabine-based intensive I-C regimens, decitabine was administered as a maintenance agent in those who had persistent MRD positivity by polymerase chain reaction analysis and/or had failed to receive all the planned cycles of consolidation therapy. Among 23 patients with MRD at the initiation of maintenance, 12 (52%) attained complete molecular response with a median molecular RFS of 93 months; for all the patients who attained or maintained a complete molecular response (n=20) the median molecular RFS was 94 months.[72] Further trials with MRD-based HMA maintenance in CBF-AML are required to better understand the benefit of this strategy.

Combinations with hypomethylating agents

Venetoclax combined with azacitidine is being studied for maintenance of remission in non-HSCT and post-HSCT settings. In the first-of-its-kind trial from the MDACC, the venetoclax (400 mg on days 1-14) - azacitidine (50 mg/m^2 on days 1-5) regimen given every 28 days for up to 24 cycles was studied in patients ≥18 years of age not immediately eligible for HSCT and in CR/CRi following two or more cycles of intensive chemotherapy or following low-intensity therapy.[73] In the last updated report of this single-arm trial (median follow-up: 13 months), among 34 patients, 25 after intensive therapy and nine after low-intensity therapy, 12-month RFS rates were 70% and 58%, respectively, and there were no deaths in remission.

The VIALE-M (NCT04102020) is a phase III randomized

controlled trial designed to compare the maintenance combination of CC-486 and venetoclax to observation in adult patients with AML in CR/CRi after intensive therapy and ineligible for HSCT with a primary aim of RFS benefit.[74] The randomization will be stratified based on age, cytogenetic risk and MRD at maintenance therapy initiation, which will likely add to the existing knowledge of efficacy of maintenance therapy in different settings.

In the post-HSCT setting venetoclax (100 mg days 1-7, later amended to 50 mg with concomitant posaconazole) - azacitidine (32 mg/m^2 days 1-5) every 28 days as maintenance was studied in 30 patients (27 with AML and 3 with T-cell acute lymphoblastic leukemia) from an ongoing phase II trial. At a median follow-up of 9 months, 12-month RFS and OS were 69% and 90%, respectively. Separate data for the AML cohort were not reported.[75] Cytopenia was significant with 30% of patients requiring venetoclax dose modifications; however, there was only one graft failure. In another study from China in patients with high-risk MDS/AML, low-dose decitabine (15 mg/m^2 for 3 days) and venetoclax (200 mg for 21 days) repeated every 2 months for ten cycles from day +100 after HSCT resulted in a 2-year EFS and OS of 85%. The regimen was reasonably well tolerated with no greater than grade 3 adverse events.[76]

An azacitidine plus lenalidomide combination has been studied as maintenance therapy in high-risk AML patients and showed acceptable tolerability but not efficacy.[77-79] In the GOELAMS group trial that included 117 high-risk AML patients, azacitidine was alternated with lenalidomide for a total of 12 cycles; 65 patients who reached CR after intensive chemotherapy received the combination which led to a median remission duration of 7 months and 2-year OS of 21% for the whole group.[78] In another study from Australia, the drugs were given in combination to 60 patients with high-risk AML in first or second CR; the median RFS was approximately 12 months.[79]

With more widespread incorporation of venetoclax into frontline intensive and low-intensity therapy algorithms for AML it remains to be studied whether further maintenance therapy containing venetoclax beyond remission induction is of potential benefit to prolong LFS. Another question is whether venetoclax should be used as part of maintenance or reserved for salvage therapy at relapse. However, considering the relatively lower efficacy of venetoclax in the relapse setting, the former approach may be more desirable.

Targeted therapy

The first in the sequence of trials on targeted therapy was the SWOG S0106 trial, reported in 2013, which failed to show any benefit from post-consolidation gemtuzumab ozogamicin (an anti-CD33 antibody-drug conjugate) as maintenance therapy *versus* observation.[80]

FLT3 inhibitors

The SORAML study, conducted in adult patients with AML irrespective of FLT3 status, was the first to compare the addition of sorafenib (400 mg twice daily) to intensive I-C chemotherapy or the same therapy plus placebo followed by maintenance sorafenib or placebo for 12 months. The trial showed an improvement in EFS in the sorafenib arm (3-year EFS: 40% *vs*. 22%) but no difference in OS.[81] However, the trial was not powered to study specifically the impact of sorafenib maintenance.

The landmark phase III RATIFY trial evaluated the addition of midostaurin or placebo to intensive I-C therapy followed by maintenance (50 mg twice a day for 12 cycles of 28 days each) in 717 adult patients with *FLT3*-mutated, newly diagnosed AML.[82] Patients in the midostaurin arm had a superior 4-year EFS (28.2% *vs*. 20.6%) and OS (51.4% *vs*. 44.3%), when not censored for SCT, leading to approval of the drug as an add-on to intensive I-C therapy by the US Food and Drug Administration, but not for maintenance. Indeed, the trial was not powered to assess the efficacy of the drug as a maintenance agent and no randomization was done at the time of maintenance. In a *post-hoc* landmark analysis to understand the impact on survival, both during maintenance and at 1 year after the end of maintenance, DFS (75% *vs*. 91%) was not different between the midostaurin and placebo arms.[83] In a concurrent phase II trial in adult patients with *FLT3*-ITD AML, conducted by Schlenk and colleagues from the German-Austrian AML group, midostaurin was added during intensive I-C and continued as maintenance (50 mg twice daily for 1 year) after chemotherapy or HSCT. Overall, 34% of the 284 patients proceeded to midostaurin maintenance; the 2-year EFS and OS were 34-39% and 46-53% in the older and younger patients, respectively. Among the patients who proceeded to HSCT in first remission and were event-free by day 100, a landmark analysis showed superior EFS and OS in those who started midostaurin within 100 days of transplant (n=71) than in those who did not receive maintenance (n=45).[84]

The phase III ADMIRAL trial led to the approval of gilteritinib as monotherapy in adult patients with relapsed or refractory *FLT3*-ITD/tyrosine kinase domain-mutated AML.[85] In a long-term follow-up (37 months) of the trial, continued gilteritinib therapy preserved the superior OS (2-year OS: 20.6% *vs*. 14.2%).[86] In the QuANTUM First trial, the addition of quizartinib to intensive chemotherapy followed by maintenance in patients with *FLT3*-ITD AML improved RFS and OS; detailed reporting of the maintenance data is awaited but the strategy could provide an additional option for *FLT3*-ITD AML.[87] The use of FLT3 inhibitors after HSCT will be discussed separately.

IDH inhibitors and other targeted therapies

Although data on the continued use of IDH inhibitors as

maintenance in the non-HSCT setting are not yet mature, these agents hold tremendous promise given their potency in *IDH*-mutated leukemia (with azacitidine), tolerability, and ease of administration.[88,89] In a phase I study, ivosidenib (n=60) or enasidenib (n=91) was added to intensive I-C chemotherapy and continued as a maintenance agent until relapse, toxicity or HSCT.[90] The trial showed the feasibility of such an approach and led to a 12-month OS of 75% in the two cohorts, although the DFS or OS benefit from the maintenance standpoint cannot be commented upon.

Dasatinib has been studied as add-on to intensive chemotherapy followed by maintenance (usually at 100 mg/day for 1 year) in CBF-AML, primarily aiming to ameliorate the negative impact of kinase mutations in these patients. With this approach the AMLSG 11-08 trial documented a 4-year cumulative incidence of relapse of 33% and OS of 75% in 89 patients with CBF-AML.[91] The CALGB 10801 trial showed 3-year DFS and OS rates of 75% and 77%, respectively, in 61 patients with CBF-AML with the addition of dasatinib.[92] Neither of these trials used gemtuzumab ozogamicin during the I-C; the negative impact of kinase mutations in CBF-AML with fludarabine – high-dose cytarabine-based therapy along with gemtuzumab ozogamicin may be diminished and thus additional benefit/toxicity of dasatinib maintenance in these patients needs to be studied in randomized trials.[93]

Several other agents have been evaluated in maintenance for AML in the non-HSCT setting, including pembrolizumab,[94] androgens,[95,96] and panobinostat.[97] None of these has led to practice-changing improvements in outcomes. Only in the phase III GOELAMS randomized controlled trial, which included elderly patients with AML, did the use of norethandrolone (an anabolic steroid) lead to improved 5-year DFS (31% *vs*. 16%) and OS (26% *vs*. 17%), with the benefits being maintained even when adjusting for most baseline patient- and disease-related factors.[96]

Post-allogeneic stem cell transplantation-directed maintenance

Though there has been significant overlap in the discussion of maintenance regimens in the non-HSCT and post-HSCT settings, here we will focus on some of the more important studies conducted purely in the post-transplant setting.

FLT3 inhibitors

With regard to FLT3 inhibitors, data on sorafenib maintenance in the post-HSCT maintenance setting are the most robust. The foremost trial in this setting is the phase II SORMAIN trial that randomized 83 patients with *FLT3*-ITD AML in CR after HSCT to sorafenib maintenance (n=43) or placebo (n=40) for 2 years. The drug was well tolerated with no increased GvHD and led to improved RFS (not reached *vs*. 30.9 months) and 24-month OS (90% *vs*. 66%) at a median follow-up of 42 months.[98] A phase III randomized controlled trial from China also documented a reduced incidence of relapse (7% *vs*. 25%) with sorafenib maintenance after HSCT in *FLT3*-ITD-mutated AML without increased risks of GvHD.[99] The phase II randomized RADIUS trial failed to show any clear benefit from midostaurin maintenance (50 mg twice daily in 12 cycles each of 4 weeks) after HSCT in *FLT3*-ITD AML.[100]

There are no reported randomized data as of yet with other FLT3 inhibitors as maintenance in the post-HSCT setting but trials are ongoing. A small retrospective analysis from Japan recently described an improved LFS (100% *vs*. 36%) and OS (100% *vs*. 46%) at 1 year with gilteritinib maintenance; this improvement was greatest in those patients who had a higher disease burden at HSCT.[101] A recent press release about the phase III MORPHO trial (NCT02997202) by BMT-CTN declared that gilteritinib maintenance *versus* placebo for 2 years in AML patients with *FLT3*-ITD following HSCT failed to meet the primary endpoint of RFS benefit in the gilteritinib arm.[102,103] The full data from this trial are pending. With respect to quizartinib, the detailed data on post-HSCT maintenance from the QuANTUM First trial are pending; in the QuANTUM-R trial the patients in the quizartinib arm who underwent HSCT in composite CR and received quizartinib maintenance thereafter had a better OS than those who did not (n=31 *vs*. 11; median OS: 27 *vs*. 5.4 months).[104] Data from a *post-hoc* trial analysis and retrospective analysis with FLT3 inhibitor maintenance or with any other maintenance approach need to be studied carefully because often those patients with the highest risk disease (GvHD, cytopenia) are not able to receive the maintenance agent after HSCT and are already destined to poorer outcomes than those of the patients who are better placed to tolerate maintenance agent.[105] This might lead to false overstating of the benefit of any post-HSCT maintenance therapy.

IDH inhibitors

IDH inhibitors are being studied actively as post-HSCT maintenance; in a phase I trial in which enasidenib (planned for 1 year) was administered to 19 *IDH2*-mutated patients (17 AML, 2 MDS) after transplant, 2-year PFS and OS were 69% and 74%, respectively, with no significant safety concerns.[106] The results of a similar study with ivosidenib in *IDH1*-mutated AML/MDS are awaited (NCT03564821).

Hypomethylating agent-based therapy

A phase III randomized study by Oran *et al*. failed to show any RFS (median RFS: <2 *vs*. 1.3 years) or OS (median OS: 2.5 *vs*. 2.6 years) benefit of azacitidine maintenance (32

mg/m^2 for 5 days every 28 days, 12 cycles) over placebo after HSCT in AML.[107] Other than the reported data, the phase III randomized AMADEUS trial is comparing the efficacy and tolerability of CC-486 to placebo after HSCT in patients with AML/MDS (NCT04173533). Phase I data on this agent after HSCT showed favorable trends in GvHD incidence and relapse risks.[108] Overall, the use of parenteral azacitidine or decitabine at doses lower than recommended for MDS/AML initial therapy, administered over a fixed duration after HSCT, is feasible, does not lead to increased risks of GvHD, and is associated with reduced risks of relapse. A meta-analysis including 14 studies (not limited to randomized controlled trials) showed favorable benefits of post-HSCT HMA maintenance with regard to RFS and OS as well as reduction in rates of chronic GvHD.[109]

An important development was the recently reported, encouraging result on the use of eprenetapopt in combination with azacitidine as maintenance therapy in *TP53*-mutated MDS/AML patients after HSCT. The combination, planned to be given for 12 cycles administered every 4 weeks, led to a median RFS of 12.5 months and OS of 20.6 months (at a median follow-up of 17 months) in 33 patients (79% previously exposed to HMA, 36% with active disease at the time of HSCT, 83% with persistent *TP53* mutation at HSCT) who received this maintenance.[110] The combination was well tolerated, even from the points of view of GvHD and central nervous system toxicity.

Boosting post-transplant immune surveillance

Donor lymphocyte infusion (DLI) has been one of the most successful methods of boosting post-transplant immune surveillance.[111] Prophylactic DLI that is administered before any evidence of disease recurrence can be considered as maintenance; however, in clinical practice DLI is often a pre-emptive therapy that is used for molecular relapse or loss of donor chimerism after HSCT.[112] The lower the disease burden at DLI, the greater the extent of benefit. In multiple studies in high-risk AML, prophylactic DLI led to encouraging survival rates.[113-116] In a study by Jedlickova and colleagues, in which high-risk AML patients who received prophylactic DLI (n=46) were compared to a matched group of patients not treated with DLI (n=34), patients in the DLI arm had a superior 7-year OS of 67% compared to 31% in the latter.[115] It is important to understand that, in the absence of active GvHD, rapid tapering of immunosuppression is warranted for a better graft-*versus*-leukemia effect in patients who show any evidence of disease relapse and before DLI infusion.[116]

Multiple developments in post-HSCT adoptive cellular therapy have occurred over the last two decades, in the form of cytokine activated DLI, unmodified or chimeric antigen receptor modified natural-killer cells, chimeric antigen receptor T cells, etc. with the aim of refining the anti-leukemia activity and potentiating the graft-*versus*-leukemia effect.[111] Vaccines against specific antigens expressed by tumors have also been tried in both the non-HSCT and post-HSCT settings,[117,118] primary among which have been those against the WT1 protein in patients with *WT1*-mutated AML.[119] There have been some positive results, but randomized data are lacking.[120-123]

Conclusions

Continued post-remission therapy beyond consolidation is becoming more relevant in patients with AML. Unlike in acute lymphoblastic leukemia and acute promyelocytic leukemia, these approaches in AML have been associated with varying success. Given the biological heterogeneity of AML, the choice of maintenance therapy will likely be guided by the patient's AML genomics, remission status and transplant eligibility. Designing any maintenance therapy in AML should be considered with respect to burdens of additional toxicity, hospital visits and the patient's quality of life.

An ongoing trial at the MDACC is engaging some of the above-mentioned contexts and using a genomically inspired approach to study different combinations of oral maintenance therapy in AML (NCT 05010772). In this five parallel-arm study, adult patients with AML in first remission after intensive remission induction therapy and at least one cycle of intensive consolidation therapy (intensive induction cohort) or after at least two cycles of low-intensity therapy (lower intensity induction cohort) and not candidates for immediate HSCT will receive either oral decitabine alone, or oral decitabine with venetoclax or with a genomics-determined add-on drug (gilteritinib, enasidenib or ivosidenib) to oral decitabine as a maintenance regimen for up to 24 cycles. The trial started enrollment around a year ago.

At the MDACC, maintenance therapy is now advocated to all patients with AML as part of ongoing clinical trials. Parenteral decitabine is suggested for patients with CBF-AML when they are unable to complete designated cycles of fludarabine, cytarabine, granulocyte colony-stimulating factor and gemtuzumab ozogamicin I-C regimens or have persistent molecular MRD after adequate consolidation therapy. For patients with intermediate- and adverse-risk AML, HSCT is the preferred consolidation, followed by maintenance as considered appropriate. In patients who are not able to proceed to HSCT a combination of HMA with or without venetoclax is advocated in the absence of a targetable myeloid mutation. For patients with targetable mutations, such as *FLT3* or *IDH*, the corresponding inhibitors are continued (as monotherapy or with HMA) as a maintenance therapy after remission induction through intensive/low-intensity regimens. The duration of such maintenance therapy is variable and determined by the patient's

tolerance and blood count recovery, baseline AML genomics, MRD dynamics and possibility of subsequent HSCT.

The approaches to AML maintenance have evolved over the last 25 years from low-intensity chemotherapy to the use of more targeted therapies as well as immunotherapy. Whether any such approach truly improves OS in patients who have received adequate frontline therapy and are in a state of deep response needs to be studied better. In patients with high-risk disease (complex karyotype, *TP53* mutation, relapsed/refractory disease, MRD-positive at/after HSCT), there is little debate that most physicians would prefer a maintenance therapy. However, whether such maintenance therapy in less adverse-risk AML is beneficial will likely be determined in ongoing trials. The possibility of aggravating genomic instability and clonal escape under maintenance therapy pressure must be kept in mind when designing such regimens.

Disclosures

JS has no relevant conflicts of interest to disclose. TMK reports having received research funding from AbbVie, Amgen, BioLine Rx, Bristol-Myers Squibb, Celgene, Jazz, and Pfizer, and personal fees from AbbVie, Amgen, Genentech, Jazz, Pfizer, Pharmacyclics, and Takeda, all outside the submitted work. FR reports having received research funding from Amgen, Cyclacel, Ltd, Macrogenix, Menarini Ricerche, Selvita, and Xencor, and personal fees from Amgen, Macrogenix, and Xencor, all outside the submitted work.

Contributions

JS and FR designed the manuscript. JS made the tables and figures. JS wrote the first draft of the manuscript. TMK and FR reviewed and edited the manuscript. All authors approved the final version of the manuscript.

References

1. Cooperrider JH, Shukla N, Nawas MT, Patel AA. The cup runneth over: treatment strategies for newly diagnosed acute myeloid leukemia. JCO Oncol Pract. 2022;19(2):74-85.
2. Short NJ, Zhou S, Fu C, et al. Association of measurable residual disease with survival outcomes in patients with acute myeloid leukemia: a systematic review and meta-analysis. JAMA Oncol. 2020;6(12):1890-1899.
3. Kantarjian H, Kadia T, DiNardo C, et al. Acute myeloid leukemia: current progress and future directions. Blood Cancer J. 2021;11(2):41.
4. Burnett AK, Russell NH, Hills RK, et al. Optimization of chemotherapy for younger patients with acute myeloid leukemia: results of the Medical Research Council AML15 trial. J Clin Oncol. 2013;31(27):3360-3368.
5. Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: systematic review and meta-analysis of prospective clinical trials. JAMA. 2009;301(22):2349-2361.
6. Toksvang LN, Lee SHR, Yang JJ, Schmiegelow K. Maintenance therapy for acute lymphoblastic leukemia: basic science and clinical translations. Leukemia. 2022;36(7):1749-1758.
7. Sanz MA, Fenaux P, Tallman MS, et al. Management of acute promyelocytic leukemia: updated recommendations from an expert panel of the European LeukemiaNet. Blood. 2019;133(15):1630-1643.
8. Wei AH, Döhner H, Pocock C, et al. Oral azacitidine maintenance therapy for acute myeloid leukemia in first remission. N Engl J Med. 2020;383(26):2526-2537.
9. Jen EY, Wang X, Li M, et al. FDA approval summary: oral azacitidine for continued treatment of adults with acute myeloid leukemia unable to complete intensive curative therapy. Clin Cancer Res. 2022;28(14):2989-2993.
10. Perissinotti AJ, Benitez LL, Marini BL. Oral azacitidine maintenance for acute myeloid leukemia. N Engl J Med. 2021;384(13):e51.
11. Kadia TM, Reville PK, Wang X, et al. Phase II study of venetoclax added to cladribine plus low-dose cytarabine alternating with 5-azacitidine in older patients with newly diagnosed acute myeloid leukemia. J Clin Oncol. 2022;40(33):3848-3857.
12. DiNardo CD, Jonas BA, Pullarkat V, et al. Azacitidine and venetoclax in previously untreated acute myeloid leukemia. N Engl J Med. 2020;383(7):617-629.
13. Wei AH, Panayiotidis P, Montesinos P, et al. Long-term follow-up of VIALE-C in patients with untreated AML ineligible for intensive chemotherapy. Blood. 2022;140(25):2754-2756.
14. Heuser M, Freeman SD, Ossenkoppele GJ, et al. 2021 Update on MRD in acute myeloid leukemia: a consensus document from the European LeukemiaNet MRD Working Party. Blood. 2021;138(26):2753-2767.
15. Burnett AK, Russell NH, Hills RK, et al. A randomized comparison of daunorubicin 90 mg/m2 vs 60 mg/m2 in AML induction: results from the UK NCRI AML17 trial in 1206 patients. Blood. 2015;125(25):3878-3885.
16. Löwenberg B, Ossenkoppele GJ, van Putten W, et al. High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med. 2009;361(13):1235-1248.
17. Röllig C, Steffen B, Schliemann C, et al. Single versus double induction with "7+3" containing 60 versus 90 mg daunorubicin for newly diagnosed AML: results from the randomized controlled SAL dauno-double trial. Blood. 2022;140(Suppl 1):523-525.
18. Krug U, Berdel WE, Gale RP, et al. Increasing intensity of therapies assigned at diagnosis does not improve survival of adults with acute myeloid leukemia. Leukemia. 2016;30(6):1230-1236.
19. Burnett A, Russell N, Freeman S, et al. A comparison of limited consolidation chemotherapy therapy or not, and demethylation maintenance or not in older patients with AML and high risk MDS: long term results of the UK NCRI AML16 trial. Haematologica. 2015;100(Suppl 1):194.
20. Huls G, Chitu DA, Havelange V, et al. Azacitidine maintenance after intensive chemotherapy improves DFS in older AML patients. Blood. 2019;133(13):1457-1464.
21. Sauter C, Fopp M, Imbach P, et al. Acute myelogenous leukaemia: maintenance chemotherapy after early consolidation treatment does not prolong survival. Lancet.

1984;323(8373):379-382.
22. Büchner T, Urbanitz D, Hiddemann W, et al. Intensified induction and consolidation with or without maintenance chemotherapy for acute myeloid leukemia (AML): two multicenter studies of the German AML Cooperative Group. J Clin Oncol. 1985;3(12):1583-1589.
23. Robles C, Kim KM, Oken MM, et al. Low-dose cytarabine maintenance therapy vs observation after remission induction in advanced acute myeloid leukemia: an Eastern Cooperative Oncology Group trial (E5483). Leukemia. 2000;14(8):1349-1353.
24. Johnson SA, Prentice AG, Phillips MJ. Treatment of acute myeloid leukaemia with early intensive induction therapy. Acta Oncol. 1988;27(5):527-529.
25. Löwenberg B, Suciu S, Archimbaud E, et al. Mitoxantrone versus daunorubicin in induction-consolidation chemotherapy--the value of low-dose cytarabine for maintenance of remission, and an assessment of prognostic factors in acute myeloid leukemia in the elderly: final report. European Organization for the Research and Treatment of Cancer and the Dutch-Belgian Hemato-Oncology Cooperative Hovon Group. J Clin Oncol. 1998;16(3):872-881.
26. Perel Y, Auvrignon A, Leblanc T, et al. Impact of addition of maintenance therapy to intensive induction and consolidation chemotherapy for childhood acute myeloblastic leukemia: results of a prospective randomized trial, LAME 89/91. J Clin Oncol. 2002;20(12):2774-2782.
27. Malkovský M, Sondel PM. Interleukin 2 and its receptor: structure, function and therapeutic potential. Blood Rev. 1987;1(4):254-266.
28. Maraninchi D, Blaise D, Viens P, et al. High-dose recombinant interleukin-2 and acute myeloid leukemias in relapse. Blood. 1991;78(9):2182-2187.
29. Kolb HJ, Schattenberg A, Goldman JM, et al. Graft-versus-leukemia effect of donor lymphocyte transfusions in marrow grafted patients. Blood. 1995;86(5):2041-2050.
30. Speletas M, Ritis K, Bourikas G. Achievement and maintenance of complete remission in a patient with acute myelogenous leukemia after weekly administration of interleukin-2. Haematologica. 1996;81(4):346-348.
31. Tajima F, Kawatani T, Endo A, Kawasaki H. Natural killer cell activity and cytokine production as prognostic factors in adult acute leukemia. Leukemia. 1996;10(3):478-482.
32. Schliemann C, Gutbrodt KL, Kerkhoff A, et al. Targeting interleukin-2 to the bone marrow stroma for therapy of acute myeloid leukemia relapsing after allogeneic hematopoietic stem cell transplantation. Cancer Immunol Res. 2015;3(5):547-556.
33. Decot V, Voillard L, Latger-Cannard V, et al. Natural-killer cell amplification for adoptive leukemia relapse immunotherapy: comparison of three cytokines, IL-2, IL-15, or IL-7 and impact on NKG2D, KIR2DL1, and KIR2DL2 expression. Exp Hematol. 2010;38(5):351-362.
34. Sievers EL, Lange BJ, Sondel PM, et al. Feasibility, toxicity, and biologic response of interleukin-2 after consolidation chemotherapy for acute myelogenous leukemia: a report from the Children's Cancer Group. J Clin Oncol. 1998;16(3):914-919.
35. Blaise D, Attal M, Reiffers J, et al. Randomized study of recombinant interleukin-2 after autologous bone marrow transplantation for acute leukemia in first complete remission. Eur Cytokine Netw. 2000;11(1):91-98.
36. Kolitz JE, Hars V, DeAngelo DJ, et al. Phase III trial of immunotherapy with recombinant interleukin-2 (rIL-2) versus observation in patients < 60 years with acute myeloid leukemia (AML) in first remission (CR1): preliminary results from Cancer and Leukemia Group B (CALGB) 19808. Blood. 2007;110(11):157.
37. Baer MR, George SL, Caligiuri MA, et al. Low-dose interleukin-2 immunotherapy does not improve outcome of patients age 60 years and older with acute myeloid leukemia in first complete remission: Cancer and Leukemia Group B Study 9720. J Clin Oncol. 2008;26(30):4934-4939.
38. Lange BJ, Smith FO, Feusner J, et al. Outcomes in CCG-2961, a Children's Oncology Group phase 3 trial for untreated pediatric acute myeloid leukemia: a report from the Children's Oncology Group. Blood. 2008;111(3):1044-1053.
39. Pautas C, Merabet F, Thomas X, et al. Randomized study of intensified anthracycline doses for induction and recombinant interleukin-2 for maintenance in patients with acute myeloid leukemia age 50 to 70 years: results of the ALFA-9801 study. J Clin Oncol. 2010;28(5):808-814.
40. Petit A, Ducassou S, Leblanc T, et al. Maintenance therapy with interleukin-2 for childhood AML: results of ELAM02 phase III randomized trial. Hemasphere. 2018;2(6):e159.
41. Buyse M, Squifflet P, Lange BJ, et al. Individual patient data meta-analysis of randomized trials evaluating IL-2 monotherapy as remission maintenance therapy in acute myeloid leukemia. Blood. 2011;117(26):7007-7013.
42. Mao C, Fu XH, Yuan JQ, et al. Interleukin-2 as maintenance therapy for children and adults with acute myeloid leukaemia in first complete remission. Cochrane Database Syst Rev. 2015(11):CD010248.
43. Aurelius J, Martner A, Brune M, et al. Remission maintenance in acute myeloid leukemia: impact of functional histamine H2 receptors expressed by leukemic cells. Haematologica. 2012;97(12):1904-1908.
44. Brune M, Hansson M, Mellqvist UH, Hermodsson S, Hellstrand K. NK cell-mediated killing of AML blasts: role of histamine, monocytes and reactive oxygen metabolites. Eur J Haematol. 1996;57(4):312-319.
45. Mellqvist UH, Hansson M, Brune M, Dahlgren C, Hermodsson S, Hellstrand K. Natural killer cell dysfunction and apoptosis induced by chronic myelogenous leukemia cells: role of reactive oxygen species and regulation by histamine. Blood. 2000;96(5):1961-1968.
46. Brune M, Castaigne S, Catalano J, et al. Improved leukemia-free survival after postconsolidation immunotherapy with histamine dihydrochloride and interleukin-2 in acute myeloid leukemia: results of a randomized phase 3 trial. Blood. 2006;108(1):88-96.
47. Palva IP, Almqvist A, Elonen E, et al. Value of maintenance therapy with chemotherapy or interferon during remission of acute myeloid leukaemia. Eur J Haematol. 1991;47(3):229-233.
48. Jiang H, Liu X-H, Kong J, et al. Interferon-α as maintenance therapy can significantly reduce relapse in patients with favorable-risk acute myeloid leukemia. Leuk Lymphoma. 2021;62(12):2949-2956.
49. Jackson GH, Davies FE, Pawlyn C, et al. Lenalidomide maintenance versus observation for patients with newly diagnosed multiple myeloma (Myeloma XI): a multicentre, open-label, randomised, phase 3 trial. Lancet Oncol. 2019;20(1):57-73.
50. Abou Dalle I, Kantarjian HM, Ravandi F, et al. Phase 2 study of lenalidomide maintenance for patients with high-risk acute myeloid leukemia in remission. Cancer. 2021;127(11):1894-1900.
51. Löwenberg B, Pabst T, Maertens J, et al. Addition of lenalidomide to intensive treatment in younger and middle-aged adults with newly diagnosed AML: the HOVON-SAKK-132 trial. Blood Adv. 2021;5(4):1110-1121.
52. Pham B, Hoeg R, Krishnan R, Richman C, Tuscano J, Abedi M. Safety and tolerability of lenalidomide maintenance in post-transplant acute myeloid leukemia and high-risk myelodysplastic syndrome. Bone Marrow Transplant.

2021;56(12):2975-2980.
53. Ansell SM, Lesokhin AM, Borrello I, et al. PD-1 blockade with nivolumab in relapsed or refractory Hodgkin's lymphoma. N Engl J Med. 2014;372(4):311-319.
54. Kuruvilla J, Ramchandren R, Santoro A, et al. Pembrolizumab versus brentuximab vedotin in relapsed or refractory classical Hodgkin lymphoma (KEYNOTE-204): an interim analysis of a multicentre, randomised, open-label, phase 3 study. Lancet Oncol. 2021;22(4):512-524.
55. Jain N, Senapati J, Thakral B, et al. A phase 2 study of nivolumab combined with ibrutinib in patients with diffuse large B-cell Richter transformation of CLL. Blood Adv. 2023;7(10):1958-1966.
56. Robert C, Schachter J, Long GV, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521-2532.
57. Robert C. A decade of immune-checkpoint inhibitors in cancer therapy. Nat Commun. 2020;11(1):3801.
58. Wei SC, Duffy CR, Allison JP. Fundamental mechanisms of immune checkpoint blockade therapy. Cancer Discov. 2018;8(9):1069-1086.
59. Reville PK, Kantarjian HM, Ravandi F, et al. Nivolumab maintenance in high-risk acute myeloid leukemia patients: a single-arm, open-label, phase II study. Blood Cancer J. 2021;11(3):60.
60. Liu H, Sharon E, Karrison TG, et al. Randomized phase II study to assess the role of nivolumab as single agent to eliminate minimal residual disease and maintain remission in acute myelogenous leukemia (AML) patients after chemotherapy (NCI9706 protocol; REMAIN trial). Blood. 2022;140(Suppl 1):1716-1719.
61. Davids MS, Kim HT, Costello C, et al. A multicenter phase 1 study of nivolumab for relapsed hematologic malignancies after allogeneic transplantation. Blood. 2020;135(24):2182-2191.
62. Wang AY, Kline J, Stock W, et al. Unexpected toxicities when nivolumab was given as maintenance therapy following allogeneic stem cell transplantation. Biol Blood Marrow Transplant. 2020;26(5):1025-1027.
63. Ravandi F, Assi R, Daver N, et al. Idarubicin, cytarabine, and nivolumab in patients with newly diagnosed acute myeloid leukaemia or high-risk myelodysplastic syndrome: a single-arm, phase 2 study. Lancet Haematol. 2019;6(9):e480-e488.
64. Penter L, Liu Y, Wolff JO, et al. Mechanisms of response and resistance to combined decitabine and ipilimumab for advanced myeloid disease. Blood. 2023;141(15):1817-1830.
65. Wolf Y, Anderson AC, Kuchroo VK. TIM3 comes of age as an inhibitory receptor. Nat Rev Immunol. 2020;20(3):173-185.
66. Majeti R, Chao MP, Alizadeh AA, et al. CD47 is an adverse prognostic factor and therapeutic antibody target on human acute myeloid leukemia stem cells. Cell. 2009;138(2):286-299.
67. Boumber Y, Kantarjian H, Jorgensen J, et al. A randomized study of decitabine versus conventional care for maintenance therapy in patients with acute myeloid leukemia in complete remission. Leukemia. 2012;26(11):2428-2431.
68. Blum W, Sanford BL, Klisovic R, et al. Maintenance therapy with decitabine in younger adults with acute myeloid leukemia in first remission: a phase 2 Cancer and Leukemia Group B study (CALGB 10503). Leukemia. 2017;31(1):34-39.
69. Foran JM, Sun Z, Claxton DF, et al. Maintenance decitabine (DAC) improves disease-free (DFS) and overall survival (OS) after intensive therapy for acute myeloid leukemia (AML) in older adults, particularly in FLT3-ITD-negative patients: ECOG-ACRIN (E-A) E2906 randomized study. Blood. 2019;134(Suppl_1):115.
70. Borthakur G, Ravandi F, Patel K, et al. Retrospective comparison of survival and responses to fludarabine, cytarabine, GCSF (FLAG) in combination with gemtuzumab ozogamicin (GO) or idarubicin (IDA) in patients with newly diagnosed core binding factor (CBF) acute myelogenous leukemia: MD Anderson experience in 174 patients. Am J Hematol. 2022;97(11):1427-1434.
71. Yin JAL, O'Brien MA, Hills RK, Daly SB, Wheatley K, Burnett AK. Minimal residual disease monitoring by quantitative RT-PCR in core binding factor AML allows risk stratification and predicts relapse: results of the United Kingdom MRC AML-15 trial. Blood. 2012;120(14):2826-2835.
72. Senapati J, Shoukier M, Garcia-Manero G, et al. Activity of decitabine as maintenance therapy in core binding factor acute myeloid leukemia. Am J Hematol. 2022;97(5):574-582.
73. Bazinet A, Kantarjian H, Borthakur G, et al. A phase II study of azacitidine plus venetoclax as maintenance therapy in acute myeloid leukemia: durable responses with longer term follow-up. Blood. 2022;140(Suppl 1):9005-9007.
74. Ivanov V, Yeh S-P, Mayer J, et al. Design of the VIALE-M phase III trial of venetoclax and oral azacitidine maintenance therapy in acute myeloid leukemia. Future Oncol. 2022;18(26):2879-2889.
75. Oran B, Champlin RE, Thall PF, et al. Phase II trial of venetoclax (Ven) in combination with azacitidine (AZA) as maintenance therapy for high-risk acute leukemia following allogeneic stem cell transplantation (SCT). Blood. 2022;140(Suppl 1):10561-10562.
76. Wei Y, Xiong X, Li X, et al. Low-dose decitabine plus venetoclax is safe and effective as post-transplant maintenance therapy for high-risk acute myeloid leukemia and myelodysplastic syndrome. Cancer Sci. 2021;112(9):3636-3644.
77. Ramsingh G, Westervelt P, Cashen AF, et al. A phase 1 study of concomitant high-dose lenalidomide and 5-azacitidine induction in the treatment of AML. Leukemia. 2013;27(3):725-728.
78. Hunault M, Maillard N, Tanguy-Schmidt A, et al. Safety and long-term efficacy of maintenance therapy with alternating azacytidine (AZA) and lenalidomide (Len) cycles in elderly (≥ 60) fit patients (Pts) with poor prognosis AML in first complete remission (CR) after LIA induction. A phase II multicentric GOELAMS trial. Blood. 2015;126(23):3787.
79. Wei A, Tan P, Perruzza S, et al. Maintenance lenalidomide in combination with 5-azacitidine as post-remission therapy for acute myeloid leukaemia. Br J Haematol. 2015;169(2):199-210.
80. Petersdorf SH, Kopecky KJ, Slovak M, et al. A phase 3 study of gemtuzumab ozogamicin during induction and postconsolidation therapy in younger patients with acute myeloid leukemia. Blood. 2013;121(24):4854-4860.
81. Röllig C, Serve H, Hüttmann A, et al. Addition of sorafenib versus placebo to standard therapy in patients aged 60 years or younger with newly diagnosed acute myeloid leukaemia (SORAML): a multicentre, phase 2, randomised controlled trial. Lancet Oncol. 2015;16(16):1691-1699.
82. Stone RM, Mandrekar SJ, Sanford BL, et al. Midostaurin plus chemotherapy for acute myeloid leukemia with a FLT3 mutation. N Engl J Med. 2017;377(5):454-464.
83. Larson RA, Mandrekar SJ, Sanford BL, et al. An analysis of maintenance therapy and post-midostaurin outcomes in the international prospective randomized, placebo-controlled, double-blind trial (CALGB 10603/RATIFY [Alliance]) for newly diagnosed acute myeloid leukemia (AML) patients with FLT3 mutations. Blood. 2017;130(Suppl 1):145.
84. Schlenk RF, Weber D, Fiedler W, et al. Midostaurin added to chemotherapy and continued single-agent maintenance therapy in acute myeloid leukemia with FLT3-ITD. Blood. 2019;133(8):840-851.
85. Perl AE, Martinelli G, Cortes JE, et al. Gilteritinib or

chemotherapy for relapsed or refractory FLT3-mutated AML. N Engl J Med. 2019;381(18):1728-1740.
86. Perl AE, Larson RA, Podoltsev NA, et al. Follow-up of patients with R/R FLT3-mutation–positive AML treated with gilteritinib in the phase 3 ADMIRAL trial. Blood. 2022;139(23):3366-3375.
87. Erba H, Montesinos P, Vrhovac R, et al. AML-029 quizartinib prolonged overall survival (OS) vs placebo plus intensive induction and consolidation therapy followed by single-agent continuation in patients aged 18-75 years with newly diagnosed FLT3-internal tandem duplication positive (FLT3-ITD+) acute myeloid leukemia (AML). Clin Lymphoma, Myeloma Leuk. 2022;22:S208-S209.
88. Montesinos P, Recher C, Vives S, et al. Ivosidenib and azacitidine in IDH1-mutated acute myeloid leukemia. N Engl J Med. 2022;386(16):1519-1531.
89. DiNardo CD, Schuh AC, Stein EM, et al. Enasidenib plus azacitidine versus azacitidine alone in patients with newly diagnosed, mutant-IDH2 acute myeloid leukaemia (AG221-AML-005): a single-arm, phase 1b and randomised, phase 2 trial. Lancet Oncol. 2021;22(11):1597-1608.
90. Stein EM, DiNardo CD, Fathi AT, et al. Ivosidenib or enasidenib combined with intensive chemotherapy in patients with newly diagnosed AML: a phase 1 study. Blood. 2021;137(13):1792-1803.
91. Paschka P, Schlenk RF, Weber D, et al. Adding dasatinib to intensive treatment in core-binding factor acute myeloid leukemia - results of the AMLSG 11-08 trial. Leukemia. 2018;32(7):1621-1630.
92. Marcucci G, Geyer S, Laumann K, et al. Combination of dasatinib with chemotherapy in previously untreated core binding factor acute myeloid leukemia: CALGB 10801. Blood Adv. 2020;4(4):696-705.
93. Senapati J, Abuasab T, Haddad FG, et al. Common kinase mutations do not impact optimal molecular responses in core binding factor acute myeloid leukemia treated with fludarabine, cytarabine, and G-CSF based regimens. Am J Hematol. 2023;98(3):E53-E56.
94. Zeidner JF, Vincent BG, Ivanova A, et al. Phase II trial of pembrolizumab after high-dose cytarabine in relapsed/refractory acute myeloid leukemia. Blood Cancer Discov. 2021;2(6):616-629.
95. Zheng F, Li Q, Yang S, et al. Maintenance therapy with combination of azacitidine, danazol and thalidomide after intensive chemotherapy in acute myeloid leukemia patients. Blood. 2022;140(Suppl 1):11720-11722.
96. Pigneux A, Béné MC, Guardiola P, et al. Addition of androgens improves survival in elderly patients with acute myeloid leukemia: a GOELAMS study. J Clin Oncol. 2017;35(4):387-393.
97. Ocio EM, Herrera P, Olave MT, et al. Panobinostat as part of induction and maintenance for elderly patients with newly diagnosed acute myeloid leukemia: phase Ib/II panobidara study. Haematologica. 2015;100(10):1294-1300.
98. Burchert A, Bug G, Fritz LV, et al. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). J Clin Oncol. 2020;38(26):2993-3002.
99. Xuan L, Wang Y, Huang F, et al. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. Lancet Oncol. 2020;21(9):1201-1212.
100. Maziarz RT, Levis M, Patnaik MM, et al. Midostaurin after allogeneic stem cell transplant in patients with FLT3-internal tandem duplication-positive acute myeloid leukemia. Bone Marrow Transplant. 2021;56(5):1180-1189.
101. Terao T, Matsuoka K-i, Ueda H, et al. Gilteritinib maintenance therapy post-allogenic stem-cell transplantation improves the prognosis of patients with FLT3-mutated AML. Blood. 2022;140(Suppl 1):3290-3291.
102. Levis MJ, Hamadani M, Logan BR, et al. BMT CTN protocol 1506: a phase 3 trial of gilteritinib as maintenance therapy after allogeneic hematopoietic stem cell transplantation in patients with FLT3-ITD+ AML. Blood. 2019;134(Suppl_1):4602.
103. Astellas and BMT CTN Announce Topline Results from Phase 3 MORPHO Trial of Gilteritinib [press release]. Tokyo and Rockville, Maryland: Astellas Pharma Inc. and BMT CTN March 9, 2023.
104. Cortes JE, Khaled S, Martinelli G, et al. Quizartinib versus salvage chemotherapy in relapsed or refractory FLT3-ITD acute myeloid leukaemia (QuANTUM-R): a multicentre, randomised, controlled, open-label, phase 3 trial. Lancet Oncol. 2019;20(7):984-997.
105. Senapati J, Kadia TM. Which FLT3 inhibitor for treatment of AML? Curr Treat Options Oncol. 2022;23(3):359-380.
106. Fathi AT, Kim HT, Soiffer RJ, et al. Enasidenib as maintenance following allogeneic hematopoietic cell transplantation for IDH2-mutated myeloid malignancies. Blood Adv. 2022;6(22):5857-5865.
107. Oran B, de Lima M, Garcia-Manero G, et al. A phase 3 randomized study of 5-azacitidine maintenance vs observation after transplant in high-risk AML and MDS patients. Blood Adv. 2020;4(21):5580-5588.
108. de Lima M, Oran B, Papadopoulos EB, et al. CC-486 (oral azacitidine) maintenance therapy is well tolerated after allogeneic hematopoietic stem cell transplantation (alloHSCT) in patients with myelodysplastic syndromes (MDS) or acute myeloid leukemia (AML). Biology Blood Marrow Transplant. 2016;22(3):S312-S313.
109. Kungwankiattichai S, Ponvilawan B, Roy C, Tunsing P, Kuchenbauer F, Owattanapanich W. Maintenance with hypomethylating agents after allogeneic stem cell transplantation in acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. Front Med (Lausanne). 2022;9:801632.
110. Mishra A, Tamari R, DeZern AE, et al. Eprenetapopt plus azacitidine after allogeneic hematopoietic stem-cell transplantation for TP53-mutant acute myeloid leukemia and myelodysplastic syndromes. J Clin Oncol. 2022;40(34):3985-3993.
111. Biederstädt A, Rezvani K. How I treat high-risk acute myeloid leukemia using preemptive adoptive cellular immunotherapy. Blood. 2023;141(1):22-38.
112. Schmid C, Labopin M, Schaap N, et al. Long-term results and GvHD after prophylactic and preemptive donor lymphocyte infusion after allogeneic stem cell transplantation for acute leukemia. Bone Marrow Transplant. 2022;57(2):215-223.
113. Schmid C, Schleuning M, Tischer J, et al. Early allo-SCT for AML with a complex aberrant karyotype - results from a prospective pilot study. Bone Marrow Transplant. 2012;47(1):46-53.
114. Schmid C, Schleuning M, Ledderose G, Tischer J, Kolb H-J. Sequential regimen of chemotherapy, reduced-intensity conditioning for allogeneic stem-cell transplantation, and prophylactic donor lymphocyte transfusion in high-risk acute myeloid leukemia and myelodysplastic syndrome. J Clin Oncol. 2005;23(24):5675-5687.
115. Jedlickova Z, Schmid C, Koenecke C, et al. Long-term results of adjuvant donor lymphocyte transfusion in AML after allogeneic stem cell transplantation. Bone Marrow Transplant. 2016;51(5):663-667.
116. Tsirigotis P, Byrne M, Schmid C, et al. Relapse of AML after

hematopoietic stem cell transplantation: methods of monitoring and preventive strategies. A review from the ALWP of the EBMT. Bone Marrow Transplant. 2016;51(11):1431-1438.
117. Vago L, Gojo I. Immune escape and immunotherapy of acute myeloid leukemia. J Clin Invest. 2020;130(4):1552-1564.
118. Barbullushi K, Rampi N, Serpenti F, et al. Vaccination therapy for acute myeloid leukemia: where do we stand? Cancers (Basel). 2022;14(12):2994.
119. Fujii S-i, Kawamata T, Shimizu K, et al. Reinvigoration of innate and adaptive immunity via therapeutic cellular vaccine for patients with AML. Mol Ther Oncolytics. 2022;27:315-332.
120. Di Stasi A, Jimenez AM, Minagawa K, Al-Obaidi M, Rezvani K. Review of the results of WT1 peptide vaccination strategies for myelodysplastic syndromes and acute myeloid leukemia from nine different studies. Front Immunol. 2015;6:36.
121. Anguille S, Van de Velde AL, Smits EL, et al. Dendritic cell vaccination as postremission treatment to prevent or delay relapse in acute myeloid leukemia. Blood. 2017;130(15):1713-1721.
122. Maslak PG, Dao T, Bernal Y, et al. Phase 2 trial of a multivalent WT1 peptide vaccine (galinpepimut-S) in acute myeloid leukemia. Blood Adv. 2018;2(3):224-234.
123. Kreutmair S, Pfeifer D, Waterhouse M, et al. First-in-human study of WT1 recombinant protein vaccination in elderly patients with AML in remission: a single-center experience. Cancer Immunol Immunother. 2022;71(12):2913-2928.