



Measurable residual disease-guided interventions in patients with acute myeloid leukaemia undergoing allogeneic haematopoietic cell transplantation: best practice recommendations from the European Society for Blood and Marrow Transplantation Practice Harmonisation and Guidelines Committee

Jaime Sanz, Gesine Bug, Fabio Ciceri, Charles Craddock, Richard Dillon, Jordi Esteve, Matteo Giovanni Della Porta, Michael Heuser, David C de Leeuw, Arnon Nagler, Francesco Onida, Gail J Roboz, Annalisa Ruggeri, Isabel Sánchez-Ortega, Micha Srour, Ibrahim Yakoub-Agha, Francesco Buccisano

Measurable residual disease (MRD) is a key predictor of relapse, the primary cause of treatment failure after allogeneic haematopoietic cell transplantation (allo-HCT) in acute myeloid leukaemia. This Policy Review, based on guidance from the European Society for Blood and Marrow Transplantation, provides practical recommendations for incorporating MRD assessment into clinical decision making during the transplantation process, the application of which remains challenging in acute myeloid leukaemia due to technical limitations and the limited availability of standardised, evidence-based approaches. Available methods include reverse transcription quantitative PCR, digital droplet PCR, next-generation sequencing, and multiparametric flow cytometry—chimerism-based approaches are under investigation. This Policy Review highlights the importance of MRD monitoring to enable timely, risk-adapted interventions that encompass both pre-transplantation and post-transplantation periods and can include tailoring conditioning intensity, donor selection, immunosuppression management, donor lymphocyte infusions, and pharmacological therapies such as FLT3 or IDH inhibitors, hypomethylating agents, venetoclax, or menin inhibitors. These recommendations aim to harmonise MRD-driven clinical practice and improve patient outcomes, while identifying key areas for future research.

Introduction

Measurable residual disease (MRD) is a powerful biomarker for guiding therapy in patients with acute myeloid leukaemia,^{1–3} particularly because of its capacity to predict relapse and allow timely administration of allogeneic haematopoietic cell transplantation (allo-HCT) in patients at high risk. Furthermore, given that relapse remains the leading cause of treatment failure after allo-HCT, accurate MRD assessment is crucial for designing personalised interventions to enhance antileukaemic effectiveness and improve transplantation outcomes.

Therapeutic strategies guided by MRD have proven highly effective in various haematological disorders, especially with the availability of targeted treatments. However, the application of MRD assessment for clinical decision making is challenged by technical limitations and a dearth of evidence supporting MRD-driven interventions in the setting of acute myeloid leukaemia.⁴ The wide variability of techniques and threshold values used in different centres further hampers this situation.⁵ National recommendations for the monitoring, treatment, and prevention of leukaemia relapse after allo-HCT were published in 2024, and have proven valuable for standardising clinical practice.⁶ However, large variability in transplantation procedures and drug availability in different regions continue to hinder broad implementation.

In this Policy Review, the challenges and opportunities associated with MRD assessment in acute myeloid leukaemia within the allo-HCT setting are evaluated from the perspective of the European Society for Blood and Marrow Transplantation (EBMT) Practice Harmonisation and Guidelines Committee. Despite the limited availability of high-quality evidence, we aim to provide specific and practical recommendations regarding MRD monitoring to improve transplantation outcomes. The methodological aspects of various MRD evaluation techniques are first addressed, and potential MRD-guided interventions at different timepoints during the haematopoietic cell transplantation (HCT) process are then discussed. We address several key questions regarding the role of MRD-guided interventions in patients with acute myeloid leukaemia undergoing allo-HCT: (1) how should MRD be best assessed? (2) What MRD-guided interventions are available in the allo-HCT setting? (3) How does MRD assessment after chemotherapy inform the decision to proceed with allo-HCT? (4) What is the prognostic importance of MRD detection before allo-HCT, and how should detection influence transplantation decision making? (5) What is the role of MRD monitoring after allo-HCT, and how can monitoring be used to guide therapeutic interventions and improve post-transplantation outcomes?

The consensus recommendations were developed following the methodology established by the EBMT

Lancet Oncol 2025; 26: e586–96

Haematology Department, Hospital Universitari i Politècnic La Fe, Valencia Department de Medicina, Universitat de Valencia, Valencia, Spain (Prof J Sanz MD); CIBERONC, Instituto Carlos III, Madrid, Spain (J Sanz); Department of Medicine, Haematology and Oncology, Goethe University, Frankfurt, Germany (G Bug MD); Frankfurt Cancer Institute, Goethe University, Frankfurt, Germany (G Bug); German Cancer Consortium (DKTK), Partner Site Frankfurt/Mainz, Frankfurt, Germany (G Bug); German Cancer Research Center (DKFZ), Heidelberg, Germany (G Bug); Haematology and Bone Marrow Transplant Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy (Prof F Ciceri MD, A Ruggeri MD); Department of Hematology, Vita-Salute San Raffaele University, Milan, Italy (F Ciceri); Clinical Trials Unit, Warwick Medical School, University of Warwick, Coventry, UK, (Prof C Craddock MD); Centre for Clinical Haematology, University Hospitals Birmingham, Birmingham, UK (C Craddock); Department of Haematology, Guy's and St Thomas' NHS Foundation Trust, London, UK (R Dillon MD); Cancer Genetics Laboratory, Department of Medical and Molecular Genetics, King's College London, London, UK (R Dillon); Haematology Department, IDIBAPS, Hospital Clinic of Barcelona, University of Barcelona, Barcelona, Spain (J Esteve MD); Comprehensive Cancer Center, IRCCS

Humanitas Clinical & Research Center, and Department of Biomedical Sciences, Humanitas University, Milan, Italy (Prof M G Della Porta MD); Department of Haematology, Haemostasis, Oncology, and Stem Cell Transplantation, Hannover Medical School, Hannover, Germany (M Heuser MD); University Hospital Halle, Department of Internal Medicine IV, Martin-Luther-University Halle-Wittenberg, Halle, Germany (M Heuser); Department of Haematology, Amsterdam University Medical Centers, Cancer Center Amsterdam, Amsterdam, Netherlands (D C de Leeuw MD); Division of Haematology, Sheba Medical Center, Tel Aviv University, Ramat Gan, Israel (Prof A Nagler MD); Haematology and BMT Unit, ASST Fatebenefratelli-Sacco, Department of Oncology and Haemato-Oncology, University of Milan, Milan, Italy (F Onida MD); Weill Cornell Medicine, The New York Presbyterian Hospital, New York, NY, USA (Prof G J Roboz MD); EBMT Executive Office, Barcelona, Spain (I Sánchez-Ortega MD); Department of Haematology, CHU de Lille, University of Lille, INSERM U1286, Lille, France (M Srouf MD)

Practice Harmonisation Committee, with the aim of providing clear and practical guidance in areas where international consensus is lacking.⁷

Workshop recommendations

In the context of allo-HCT, MRD measurement throughout a patient’s treatment journey can be done at various timepoints, each serving distinct purposes, with different techniques—potentially prompting different interventions (figure). MRD assessment after initial chemotherapy helps establish eligibility for allo-HCT, pre-HCT MRD evaluation provides insight into the risk of post-HCT relapse, and post-HCT MRD monitoring is crucial for early relapse detection. Based on a review of the technical aspects of MRD monitoring and the spectrum of potential interventions, specific recommendations for MRD-guided interventions at each timepoint are provided.

Techniques used for MRD evaluation

MRD in acute myeloid leukaemia can be assessed with various high sensitivity molecular assays, including reverse transcription quantitative PCR (RT-qPCR), digital droplet PCR (ddPCR), error-corrected next-generation sequencing (NGS), and multiparameter flow cytometry (MFC).^{1,8} Selection of the most appropriate method depends on the biological characteristics of acute myeloid leukaemia, allowing for individualised patient monitoring. Recommendations for technique selection might evolve as new data emerge supporting the use of additional molecular markers and subgroups.

For specific molecularly defined acute myeloid leukaemia subtypes, such as those with *NPM1* mutations,

core-binding factor-rearranged (*CBF*) acute myeloid leukaemia (*RUNX1::RUNX1T1* or *CBFB::MYH11*), or acute promyelocytic leukaemia (*PML::RARA*), molecular MRD assessment by RT-qPCR or ddPCR is recommended. By contrast, patients who do not fall into these subgroups are typically monitored with MFC.¹ Although NGS-based MRD monitoring has substantially improved, making ultrahigh-sensitivity NGS a reliable tool in some acute myeloid leukaemia subsets (eg, *FLT3*-ITD), evidence for its wide clinical application continues to evolve.^{1,9–13}

Molecular methods

Molecular methods for MRD assessment include RT-qPCR, ddPCR, and specifically adapted NGS assays. PCR-based methods are applicable to 40–60% of acute myeloid leukaemia cases with identifiable founder genetic abnormalities, such as mutated *NPM1*, *RUNX1::RUNX1T1*, *CBFB::MYH11*, *PML::RARA*, *KMT2A::MLLT3*, *DEK::NUP214*, *BCR::ABL*, or non-leukaemia specific markers such as *WT1*. Moreover, leukaemia-specific PCR assays targeting markers such as *NPM1*, *PML::RARA*, and *CBF* are preferred over less specific markers such as *WT1* or *EV11* expression.¹

For NGS-based MRD testing, both the selection of mutations identified at diagnosis and the use of agnostic panel approaches offer distinct strengths and weaknesses. All detected mutations could be considered potential MRD markers, although caution is required with germline mutations and mutations associated with age-related clonal haematopoiesis, such as *DNMT3A*, *TET2*, and *ASXL1* (collectively known as DTA mutations).¹

Various studies support the use of error-corrected NGS for assessing the predictive value of stable mutations (present at diagnosis), gained mutations (emerging at relapse), and DTA mutations after HCT. Both DTA and non-DTA mutations showed similar relapse kinetics during post-HCT follow-up.¹⁴ Another expanding area of NGS is the assessment of *FLT3*-ITD as an MRD marker. Although the clinical relevance of *FLT3*-ITD MRD monitoring has previously been limited by patient-specific duplications and potential mutation instability at relapse, NGS-based techniques with sensitivities up to 10⁻⁵ have enabled the application of this type of monitoring as a predictor of relapse, particularly in the peri-transplantation period.^{9–13}

ddPCR is a modification of quantitative PCR, in which the reaction is partitioned into thousands of individual droplets. The advantages of this technique include an increased signal-to-noise ratio and absolute quantification without the need for standard curves. This technique can be particularly useful for rare mutations, for which standard curves might not be available, or single base changes, for which standard RT-qPCR might be technically challenging or even unfeasible. Published reports have shown that ddPCR-based MRD monitoring is effective for predicting relapse when specific single

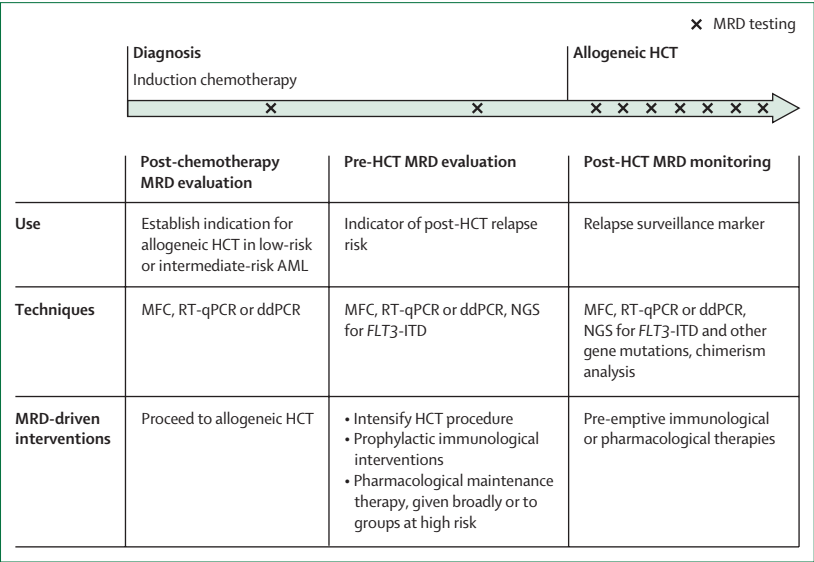


Figure: Timepoints of MRD evaluation
AML=acute myeloid leukaemia. MRD=measurable residual disease. HCT=haematopoietic cell transplantation. MFC=multiparameter flow cytometry. RT-qPCR=reverse transcription quantitative PCR. ddPCR=digital droplet PCR. NGS=next-generation sequencing.

genes as MRD markers (eg, *BCR::ABL1*, *NPM1*, *PML::RARA*, *IDH1*, *IDH2*, or *WT1*) are used in the post-transplantation setting.^{15,16}

Multiparameter flow cytometry

MFC-based MRD assessment should be performed with a validated assay and in accordance with established guidelines for the detection of rare events.^{17,18} The main strategies for assessing MRD by MFC rely on identifying leukaemia-associated immunophenotypes (eg, lineage infidelity, asynchronous marker expression, and overexpression or absence of markers) and detecting atypical immunophenotypes distinct from typical myeloid maturation patterns.^{1,19} These analytical approaches are complementary and should be combined together to ensure accurate MRD evaluation. The advantages of MFC for MRD assessment include broad applicability to approximately 90% of acute myeloid leukaemia cases in the post-transplantation setting, short turnaround time, high sensitivity (10^{-3} – 10^{-4}), and the ability to distinguish viable from non-viable cells. For reliable test sensitivity, a low limit of quantification, typically 50 residual leukaemic events in at least 500 000 total events, is required, with the ideal limit of quantification being 0.01%. Harmonisation and standardisation of MFC-based MRD have been challenging but have advanced substantially, as outlined in technical documents.¹⁹

Moreover, MFC has proven to be a reliable and standard technique for tracking leukaemic stem cells. Leukaemic stem cells typically reside in the CD34⁺CD38[−] compartment, display unique immunophenotypes not shared with typical haematopoietic stem cells, and are characterised by genetic features linked to low chemosensitivity.²⁰ Several studies have shown that leukaemic stem cell burden at diagnosis and follow-up serves as a prognostic biomarker, particularly when combined with conventional MFC MRD results.^{21,22} Ongoing research is investigating the integration of residual leukaemic stem cells assessment into MRD evaluation, which is expected to enhance prognostic accuracy in the peri-transplantation setting.

Chimerism analysis methods

The current standard for chimerism analysis is the evaluation of short tandem repeat profiles, although other DNA polymorphisms such as variable number of tandem repeats, single nucleotide polymorphisms, and insertion or deletion polymorphisms (Indel) can be used. Although short tandem repeat PCR remains the gold standard for chimerism analysis, its sensitivity is limited to 1–5%. More sensitive methods, such as RT-qPCR, ddPCR, and NGS (sensitivities ranging from 10^{-2} to 10^{-6}), are emerging and might be better suited for early interventions in haematological malignancies. A detailed discussion of the technical aspects of chimerism analysis was performed in a previous

comprehensive review²³ and is beyond the scope of these recommendations.

Chimerism measurement in both the myeloid and T-cell compartments serves two distinct purposes. Firstly, it is commonly used to assess engraftment and guide clinical interventions, such as tapering of immunosuppression, administering prophylactic donor lymphocyte infusions, providing CD34⁺ cell boosts, or performing salvage transplantation. Secondly, chimerism might function as a marker for MRD positivity. However, the role of chimerism in relapse prediction is not well defined, and its clinical utility and impact on decision making remain topics of ongoing debate. Suboptimal or declining chimerism at different timepoints was identified as an independent risk factor for relapse and impaired survival in all types of conditioning regimens in both adults and children.^{24,25} However, compared with molecular methods or MFC for MRD monitoring, chimerism status alone offers little predictive value.²⁶ For patients with a disease-specific MRD marker, early relapse detection should primarily rely on a combination of molecular assays and immunophenotyping. However, chimerism analysis can be valuable in cases for which disease-specific markers are lost at relapse. Combining sensitive chimerism analysis with MRD testing can enhance relapse prediction and improve transplantation management.²⁷ In the prospective FIGARO trial,²⁸ the negative prognostic effect associated with MRD positivity was abrogated in both study groups when full donor T-cell chimerism was maintained or reached early after transplantation. In summary, best practices for integrating chimerism analysis with MRD monitoring are still being defined since ongoing advances in technology continue to improve the sensitivity and informativity; chimerism-guided interventions remain under investigation. See panel 1 for recommendations on MRD evaluation techniques.

Definitions of MRD clinical outcomes in acute myeloid leukaemia

Definitions of clinical outcomes related to MRD assessment in patients with acute myeloid leukaemia have been previously published¹ and continue to evolve. As thresholds can change over time, the most recent European LeukemiaNet guidelines, which reflect current advances in the field, should be followed. A simplified adaptation applicable to the allo-HCT setting can be used. Complete remission with negative MRD can be defined as complete remission, complete remission with partial haematological recovery, or complete remission with incomplete haematological recovery with MRD below the defined threshold of positivity for a genetic marker, as identified by RT-qPCR, MFC, or NGS. Complete remission with positive MRD can be defined as complete remission, complete remission with partial haematological recovery, or complete remission with incomplete haematological recovery with MRD above the

Prof I Yakoub-Agha MD;
Haematology, Department of
Biomedicine and Prevention,
University Tor Vergata of
Rome, Rome, Italy
(Prof F Buccisano MD)

Correspondence to:
Prof Jaime Sanz, Haematology
Department, Hospital
Universitari i Politécnic La Fe,
Valencia Departament de
Medicina, Universitat de
Valencia, Valencia 46026, Spain
jaime.sanz@uv.es

Panel 1: Recommendations for MRD evaluation techniques***Molecular markers**

- Molecular MRD assessment by RT-qPCR is recommended for patients with *NPM1* mutations or *RUNX1::RUNX1T1*, *CBFB::MYH11*, or *PML::RARA* rearrangements.
- For patients with mutated *FLT3*-ITD and the absence of the molecular markers, ultrahigh-sensitivity NGS should be used as an alternative to MFC, when available. Current data indicate that this technique provides powerful prognostic information immediately before or after transplantation, and can guide maintenance therapy. Data on the utility of this technique for sequential monitoring are still being collected.
- Additional techniques such as ddPCR and RT-qPCR for other fusion genes have been technically validated but need further prospective clinical evaluation in terms of thresholds and informative timepoints. However, these techniques are for stable disease-specific markers and are suitable for sequential post-HCT monitoring for the early detection of relapse.

Flow cytometry

- Recommended for patients with acute myeloid leukaemia outside the aforementioned molecularly defined subgroups.

- For clinical decision making, MRD assessment should be performed with a qualified assay according to the guidelines for rare events in MFC:
 - Minimum eight colour panel.
 - Acquisition of at least 500 000–1 000 000 CD45-expressing relevant events.
 - Adequate limit of detection or limit of quantification of the assay.

Chimerism

- Chimerism analysis is not recommended as a reliable tool for MRD monitoring in patients with acute myeloid leukaemia.
- In the absence of available flow or molecular MRD techniques, chimerism analysis can provide prognostic information for predicting individual relapse risk.

MRD=measurable residual disease. RT-qPCR=reverse transcription quantitative PCR. NGS=next-generation sequencing. MFC=multiparameter flow cytometry. ddPCR=digital droplet PCR. HCT=haematopoietic cell transplantation. *The most reliable and appropriate technique should be selected based on the type of genetic lesion or atypical immunophenotype present in every individual acute myeloid leukaemia case, its stability throughout the disease course, and the level of validation of the analytical protocol used.

defined threshold of positivity for a genetic marker, as identified by RT-qPCR, MFC, or NGS. In an allo-HCT setting, complete remission with MRD positivity, even with low disease burden, can still indicate active disease and has shown prognostic relevance.^{29,30} MRD relapse can be defined as conversion from undetectable to detectable MRD or a considerable increase from the last measured nadir. The result should be rapidly verified in a second consecutive sample, preferably a bone marrow sample.

Possible MRD-guided interventions

Potential MRD-guided interventions can be categorised into three groups: (1) optimisation of the allo-HCT procedure adjusted for patients with persistent MRD at the time of transplantation; (2) immunological strategies after allo-HCT for patients with persistent MRD or those with MRD relapse; and (3) pharmacological interventions after transplantation.

Optimisation of the allo-HCT procedure

Although intensifying conditioning might enhance the antileukaemic effect of allo-HCT, it also increases non-relapse mortality, making the overall benefit in acute myeloid leukaemia a matter of debate. A phase 3 randomised trial conducted by the Blood and Marrow Transplant Clinical Trials Network showed improved relapse-free survival with myeloablative conditioning compared with reduced-intensity conditioning in patients with acute myeloid leukaemia.³¹ Interestingly, this benefit was observed only in patients with detectable

MRD before HCT, as assessed by error-corrected NGS, whereas no benefit was seen in MRD negative patients.¹² These findings align with several retrospective studies supporting the use of intensive conditioning as the standard of care for suitable patients with acute myeloid leukaemia who have pre-HCT MRD positivity.^{9,32} However, conflicting results from other studies highlight the need for further investigation. The FIGARO prospective trial examined the effects of an intensified conditioning regimen and pre-transplantation MFC MRD status on transplantation outcome.²⁸ More intense conditioning did not improve outcomes, regardless of pre-transplantation MRD status. Similarly, the BMT-CTN 1506-MORPHO trial reported improved overall survival in patients who received myeloablative conditioning compared with those who received reduced-intensity conditioning, irrespective of MRD status.¹³ Overall, these findings support the use of intensive conditioning for suitable patients with acute myeloid leukaemia, especially those with detectable MRD before HCT.

The potential to enhance the graft-versus-leukaemia (GVL) effect by donor selection remains a matter of debate. Most studies found no significant differences in relapse rates based on donor type.³³ However, particular circumstances, such as T-cell replete umbilical cord blood transplants in children,³⁴ the use of young unrelated donors,³⁵ and haploidentical donors³⁶ using post-transplantation cyclophosphamide, have been associated with reduced relapse rates. The effect of donor type on MRD status was also specifically explored in retrospective studies.^{37,38} No considerable differences in outcomes were

observed between matched siblings and matched, unrelated donor transplants.³⁹ However, some studies suggest that HLA-mismatched transplants, especially those using umbilical cord blood³⁷ or haploidentical donors,³⁸ can enhance the GVL effect and improve outcomes in patients who are MRD positive before HCT. Nevertheless, these results remain controversial, and well designed studies are needed to address the findings. Overall, the current evidence is insufficient to support a recommendation for any specific donor type based on MRD status.

Immunotherapy

Part of the antileukaemic efficacy of allo-HCT is mediated by the GVL effect, which is closely linked to graft-versus-host disease (GVHD), and contributes to reducing relapse risk in patients with acute myeloid leukaemia.^{40,41} The GVL effect is dynamic and can be modulated by various post-HCT interventions, although careful consideration is needed to balance antileukaemic efficacy with the risk of adverse effects, especially GVHD.

In terms of immunosuppression modulation, several studies suggested an association between increased exposure to calcineurin inhibitors during the initial weeks post-HCT and an elevated risk of relapse.^{42,43} This association has led to the consensus that immunosuppressive drug concentrations should be tailored to the individual patient's risk of disease recurrence. In patients at high risk, reducing the duration of immunosuppression to promote earlier acquisition of full donor T-cell chimerism mitigated the adverse effect of pre-transplantation MRD on relapse and survival²⁸ and accelerated immune recovery. Enhanced reconstitution of $\gamma\delta$ T cells after HCT was also proposed as a mechanism to help to counteract the increased relapse risk in patients with acute myeloid leukaemia who had pre-HCT MRD positivity.⁴⁴ However, this strategy should be carefully balanced against the risk of GVHD. No consensus on the optimal timing for tapering immunosuppression has been reached, with decisions often influenced by factors such as the disease status at transplantation, degree of HLA mismatch, conditioning regimen intensity, or the use of post-transplantation cyclophosphamide or in vivo T-cell depletion.

A 2024 review and consensus recommendation addressed the use of unmanipulated donor lymphocyte infusion after allo-HCT for haematological malignancies.⁴⁵ Prophylactic donor lymphocyte infusion is often offered to patients at high risk of relapse, particularly those without specific actionable targets, especially after non-myeloablative conditioning. Although small observational studies have shown encouraging results,^{46,47} well designed comparative studies are still needed. Pre-emptive donor lymphocyte infusion administered to patients in complete remission, triggered by declining chimerism or detectable MRD, aims to prevent overt relapse. As with prophylactic donor

lymphocyte infusion, some data suggest that pre-emptive donor lymphocyte infusion can offer clinical benefit.⁴⁶ A prospective study suggested that the infusion of G-CSF-mobilised peripheral blood stem cells in post-transplant patients who had MRD positivity can improve transplantation outcomes.⁴⁸ However, more robust data are needed to substantiate these findings. Donor lymphocyte infusion combined with pharmacological strategies is often recommended. Extensive research has focused on enhancing the characteristics of donor lymphocytes with various modifications to address the limitations of unmodified donor lymphocyte infusion, aiming to reduce toxicity and improve antileukaemic effectiveness.⁴⁹ However, this topic is beyond the scope of this consensus manuscript.

Post-transplantation pharmacological interventions

Post-transplantation pharmacological interventions aim to reduce relapse risk but should be balanced against potential toxicity. Two main strategies are used: maintenance therapy, given broadly or to groups at high risk (eg, MRD positive pre-HCT), although this therapy might lead to overtreatment; and pre-emptive therapy, initiated in response to early relapse markers such as post-HCT MRD, which is more targeted but relies on timely and accurate detection.

In terms of maintenance strategies, the FLT3 inhibitor sorafenib has shown efficacy in reducing relapse and improving overall survival in two randomised trials, in which it was used for universal prophylaxis, independent of MRD status.^{50,51} However, maintenance strategies post-HCT can differ based on MRD status before or after transplantation.⁵¹ Exploratory data suggest the greatest benefit from sorafenib occurs in patients who are MRD negative before HCT or MRD positive after HCT. These trials, however, included few patients and little pre-HCT FLT3 inhibitor use. A 2024 clinical trial explored the use of gilteritinib as maintenance therapy for up to 2 years in patients with FLT3-ITD acute myeloid leukaemia undergoing allo-HCT. This trial showed a clinical benefit in terms of relapse-free survival for patients with pre-HCT or post-HCT MRD positivity.¹³ MRD was assessed with a highly sensitive NGS MRD method (sensitivity up to 10^{-5} – 10^{-6}), which was able to detect any FLT3-ITD sequence, with approximately 50% of patients testing positive. Post-transplantation gilteritinib resulted in significant improvement in relapse-free survival among patients peri-transplant who were MRD positive, whereas no benefit was observed in patients who were MRD negative. These findings support an MRD-driven approach to FLT3 inhibitor maintenance, potentially sparing patients who are MRD negative from unnecessary treatment. Nonetheless, due to the limited availability of high-sensitivity NGS-based MRD testing, the need for additional supporting studies, and the proven efficacy of FLT3 inhibitors in patients who are MRD negative, maintenance strategies restricted to patients who are

MRD positive cannot yet be recommended in routine practice. Other FLT3 inhibitors, such as midostaurin and quizartinib, have not been formally evaluated in the post-HCT setting, although quizartinib has been approved for maintenance therapy after transplantation in some regions. Clinicians should exercise caution with FLT3 inhibitor maintenance due to potential unwanted drug interactions and frequent adverse conditions, such as cytopenias, which might require dose adjustments.

Post-transplant maintenance using azacitidine (a hypomethylating agent) has been difficult to implement and, so far, has not shown a clear advantage in reducing relapse rates.⁵² The AMADEUS trial (NCT04173533)—a randomised, double-blind, placebo-controlled phase 3 study—is underway, and aims to further assess the safety and efficacy of oral azacitidine as maintenance therapy in patients with MDS or acute myeloid leukaemia after HCT.

Ivosidenib (IDH1 inhibitor) and enasidenib (IDH2 inhibitor) are being explored in combination with intensive chemotherapy in the HOVON150 trial, which includes a 2 year maintenance phase. Phase 1 trials studying maintenance with enasidenib⁵³ or ivosidenib⁵⁴ after transplantation have been published, showing that the treatment is safe and well tolerated, with preliminary activity.

Further studies are warranted to identify which patients are most likely to benefit from post-allo-HCT maintenance with IDH1 or IDH2 inhibitors.

The combination of venetoclax and azacitidine has been investigated as a post-transplant maintenance strategy in a phase 1 trial, exhibiting a manageable safety profile and promising activity in patients with high-risk MDS or acute myeloid leukaemia.⁵⁵ In addition, VIALE-T is an ongoing phase 3, randomised, open-label trial (NCT04161885) evaluating the safety and efficacy of venetoclax plus azacitidine versus best supportive care as maintenance therapy after HCT in patients with acute myeloid leukaemia.

In terms of pre-emptive strategies, the RELAZA2 trial reported encouraging outcomes for patients given azacitidine who developed MRD during the post-transplant period.⁵⁶ A 2024 study showed that combining azacitidine with interferon alfa in patients with detectable MRD or loss of chimerism elicited sustained responses in a subset of patients.⁵⁷ Sorafenib monotherapy has been used for the treatment of post-transplant relapses, showing durable responses in some patients.⁵⁸ This observation was related to the induction of GVL. An experimental work showed the ability of sorafenib to increase IL-15 production, resulting in a subsequent enhancement of allogeneic CD8⁺ T-cell response.⁵⁹ No trials have yet reported on the investigation of IDH inhibitors as a potential pre-emptive intervention in patients with *IDH1*-mutated or *IDH2*-mutated acute myeloid leukaemia. The combination of venetoclax plus azacitidine has shown particular efficacy in cases of MRD failure,⁶⁰ especially among patients with *NPM1*-mutated or other favourable-risk acute myeloid leukaemia.⁶¹ The specific role of this combination in the

Panel 2: Summary of MRD-guided modification of transplant procedure and post-transplantation therapy

HCT procedure*

- A myeloablative conditioning regimen can overcome some of the poor prognostic implications of pre-HCT MRD.
- Insufficient data exist to guide GVHD prophylaxis or donor selection according to MRD.

Immunotherapy

- Antileukaemic efficacy can be modulated with immunological interventions, by reducing exposure to immunosuppressants and by use of DLI, to enhance the GVL effect.
- These interventions are commonly used in clinical practice as prophylactic or pre-emptive strategies in patients who have MRD positivity, especially in the absence of other alternatives, but evidence of efficacy is weak.
- The risk of side-effects, especially GVHD, needs to be carefully considered.

Post-transplantation pharmacological interventions

- With the growing availability of new, targeted pharmacological agents, pharmacological intervention after allo-HCT is an increasingly appealing option.
- In addition to administration as maintenance to all patients, pharmacological intervention can be guided by MRD to

both restrict prophylaxis in a selected higher-risk population who have MRD positivity pre-HCT and to guide pre-emptive therapy for those with MRD persistence or relapse.

- Post-HCT FLT3 inhibitors are safe and effective in patients with *FLT3*-mutated acute myeloid leukaemia. Sorafenib has been shown to reduce relapse independently from MRD, and gilteritinib has been shown to decrease relapse in patients with detectable MRD before or after-HCT.
- At present, insufficient data exist on the safety and efficacy of other post-transplant therapies, such as IDH inhibitors, menin inhibitors, or non-directed regimens including both venetoclax and azacitidine, to support their routine use since they remain under investigation in clinical trials. Their use might be considered in some patients who have MRD-positivity post-HCT and are showing signs of impending relapse, particularly when no alternative therapeutic options are available.

MRD=measurable residual disease. HCT=haematopoietic cell transplantation. GVHD=graft-versus-host disease. DLI=donor lymphocyte infusion. GVL=graft-versus-leukaemia. allo-HCT=allogeneic HCT. *The HCT strategy should be tailored to the individual relapse risk according to MRD status at three different stages: optimisation of the HCT procedure, immunological strategies following HCT, and pharmacological interventions.

setting of post-transplant molecular relapse has not yet been evaluated. Menin inhibitors are emerging as promising candidates for pre-emptive MRD therapy. Evidence of their benefit in the relapse and refractory setting has been observed, as they induce differentiation in *KMT2A*-rearranged and *NPM1*-mutated acute myeloid leukaemia.^{62,63} Both subgroups can be consistently monitored with molecular MRD, presenting a unique opportunity for early, orally administered intervention. However, no evidence is available regarding their use after HCT or as pre-emptive MRD therapy. See panel 2 for a summary of MRD-guided modifications.

Recommendations for MRD evaluation and MRD-guided interventions

MRD evaluation after chemotherapy as an indication for allo-HCT

Although genetic and cytogenetic profiling at diagnosis guide initial risk assessment, MRD detection after reaching morphological complete remission is crucial for evaluating the depth of disease clearance. Since baseline prognosticators often do not predict relapse, MRD has emerged as a key biomarker that can refine risk stratification, especially in patients with low-risk or intermediate-risk acute myeloid leukaemia.² MRD negativity does not necessarily indicate full disease eradication but rather that the disease is below the detection threshold of the technique used. Clinicians are encouraged to consult with their MRD laboratory experts to accurately interpret individual MRD results.¹

Panel 3: Role of MRD evaluation after chemotherapy as an indication to receive allo-HCT

- MRD positivity at crucial timepoints and thresholds can identify patients at increased risk of relapse. In specific patients with low and intermediate genetic risk, MRD positivity can be used as an indication for allo-HCT in first complete remission.
- The most important timepoints for MRD assessments, as defined by the ELN 2022 consensus recommendations, are after two cycles of intensive chemotherapy and consolidation.
- For low intensity regimens, evidence is emerging about the role of MRD in the treatment decision making process, including as a possible indication for HCT. However, decisions should also consider patient fitness and overall disease risk.
- Sequential MRD assessment after treatment completion can be useful for the early detection of relapse.
- In patients treated with non-transplantation strategies, MRD relapse during follow-up should be considered for a clinical intervention that includes allo-HCT.

MRD=measurable residual disease. allo-HCT=allogeneic haematopoietic cell transplantation. ELN=European LeukemiaNet. HCT=haematopoietic cell transplantation.

For patients with low-risk or intermediate-risk acute myeloid leukaemia receiving high-dose chemotherapy, several studies have suggested that allo-HCT can be spared in patients who reach MRD negative complete remission, overcoming the adverse prognostic effect of residual disease and providing a survival benefit in patients with MRD-positive complete remission.^{11,64} These data led to the European LeukemiaNet MRD recommendations that identify MRD assessment after two cycles of standard induction chemotherapy in patients in complete remission as a prognostic biomarker for guiding post-remission consolidation strategy.¹ Regarding patients with acute myeloid leukaemia treated with non-intensive regimens, several studies have validated the prognostic effect of MRD on survival.^{65,66} The optimal timing for MRD assessment, and its potential impact to guide additional treatment strategies that decrease relapse risk, including allo-HCT, are being evaluated. See panel 3 for the role of MRD evaluation after chemotherapy.

Role of MRD evaluation before HCT

Many studies have shown that the risk of post-transplantation relapse considerably increases in patients

Panel 4: Recommendations for pre-HCT MRD evaluation and MRD-guided interventions

MRD evaluation

- Detectable MRD does not represent a contraindication for HCT. HCT should not be delayed because of MRD positivity.
- Detectable MRD is a prognostic factor for relapse after HCT.
- Pre-transplantation MRD evaluation should be performed in all patients considered for HCT within 4 weeks of the start of conditioning.

Intervention

- Detectable MRD might help with adaptation of intensity and scheduling of immunosuppression in patients who are MRD positive.
- Intensive conditioning should be preferentially used for patients with detectable MRD who are fit.
- Immunological interventions such as early tapering of immunosuppression or prophylactic DLI can be used in patients with detectable MRD, preferentially combined with pharmacological interventions when available.
- FLT3 inhibitors should be offered as maintenance therapy in patients with FLT3-ITD+. Gilteritinib might be preferred for patients with detectable MRD.
- The recommended duration of FLT3 inhibitor maintenance therapy is 2 years. However, treatment duration should be individualised based on tolerability and patient-specific factors.

HCT=haematopoietic cell transplantation. MRD=measurable residual disease. DLI=donor lymphocyte infusion.

with detectable MRD before HCT, regardless of MRD evaluation methods used.^{10,12,28,67,68} This negative effect appears to be consistent for acute myeloid leukaemia in both first and second complete remission.⁴⁰ Notably, even the detection of low amounts of pre-HCT MRD has been associated with inferior outcomes.^{10,40} For instance, NGS-based MRD assessment showed that the persistence of *FLT3*-ITD or *NPM1* variants in the blood at an allele proportion of 0·01% or higher is associated with increased relapse risk and worse survival outcomes.¹⁰ The prognostic value of pre-HCT *NPM1* MRD assessed by RT-qPCR remains inconclusive. Although one study found no association with survival,⁶⁹ another report indicated that pre-transplantation MRD rates can predict outcomes.⁶⁸ Notably, this prognostic effect appears to be primarily confined to patients with co-occurring *FLT3*-ITD, suggesting that integrating *NPM1* MRD assessment with *FLT3*-ITD status can improve risk stratification.⁶⁸ Overall, pre-HCT MRD evaluation is a crucial timepoint, as it can inform patient discussions and influence treatment decisions.

Whether MRD reflects inherently adverse disease biology, or if the prognostic effect can be mitigated by further cytoreduction before HCT, remain unclear. No evidence supports cytoreduction before HCT, and additional therapy can compromise transplantation success.⁷⁰ This unresolved question represents a key unmet clinical need requiring further research. Therefore, HCT should probably not be delayed for patients in first

complete remission with evidence of pre-transplant MRD positivity. However, the potential clinical benefits of MRD clearance in specific scenarios, such as *NPM1*-mutated acute myeloid leukaemia, are being investigated in clinical trials. Additionally, persisting MRD after chemotherapy might be a different scenario than MRD relapse during follow-up. See panel 4 for recommendations on pre-HCT evaluation and intervention.

Role of MRD monitoring after HCT

The primary goal of post-HCT MRD monitoring is to identify patients at high risk of relapse early enough to initiate pre-emptive interventions and to prevent overt haematological relapse, which is associated with discouraging prognosis. MRD evaluation should therefore be performed in a timely manner, guided by the kinetics of the underlying disease, to enable early detection. Early post-transplant MRD evaluation can help to stratify patients according to relapse risk,⁷¹ and can offer a window for timely therapeutic intervention. In a 2024 study using ultrahigh-sensitivity NGS on peripheral blood, surveillance every 3 months detected relapse in up to 38% of cases, rising to 64% with monthly testing.¹⁴ Short intervals of serial testing and highly sensitive assays might be required for acute myeloid leukaemia with rapid kinetics, such as for patients with *FLT3* mutations.⁷²

MRD monitoring after allo-HCT remains a substantial clinical challenge. Although the presence of MRD at any timepoint after allo-HCT is a strong predictor of relapse,

Panel 5: Recommendations for post-HCT MRD evaluation and MRD-guided interventions

MRD evaluation

- MRD relapse is a marker of impending haematological relapse and poor prognosis.
- The goal of MRD-guided intervention is to allow prompt therapeutic action and reduce the risk of haematological relapse.
- Monitoring of MRD is mandatory for all patients.
- An early post-transplantation MRD evaluation is strongly recommended after engraftment and within 60 days post-HCT.
- The recommended frequency of MRD monitoring depends on the disease type, the availability of a suitable marker, and the technique used. For patients requiring bone marrow aspiration, MRD assessment every 3 months is generally advised. By contrast, for *NPM1* or *CBF* transcripts measurable in peripheral blood, more frequent monitoring might be preferable.
- Patients with detectable MRD should repeat testing in 2–4 weeks time.
- MRD monitoring should be continued for up to 2 years following HCT.
- More frequent monitoring is recommended for patients at high risk, according to ELN category, MRD positivity before and after transplantation, and MRD kinetics.

- MRD monitoring is particularly important in patients at high risk, as defined by the ELN classification, and in those who are MRD positive before or after HCT.

Intervention

- Any level of detection of post-HCT MRD should trigger specific interventions to decrease the risk of relapse.
- Therapeutic interventions should be selected according to availability and individual patients.
- For patients without GVHD and ongoing immunosuppression, early withdrawal of immunosuppression is common practice.
- For patients without GVHD and off immunosuppression, DLI is common practice.
- Targeted pharmacological agents should be used in patients for whom these therapies are available.
- Combined pharmacological and immunological strategies could be considered.
- For patients without available pharmacological targeted therapies, no data exist on prioritising non-targeted pharmacological therapies or immunological approaches.

HCT=haematopoietic cell transplantation. MRD=measurable residual disease. ELN=European LeukemiaNet. GVHD=graft-versus-host disease. DLI=donor lymphocyte infusion.

around a third of patients who are MRD positive do not relapse, whereas approximately a third of patients who are MRD negative eventually do,⁷³ underscoring the complexity of MRD interpretation in the post-transplantation setting. Lowering the threshold for MRD positivity by use of MFC has increased sensitivity at the cost of reduced specificity—innovative strategies with computational analysis can enhance evaluation capacity.⁷²

Pre-emptive interventions triggered by MRD detection are commonly used and generally recommended; however, little retrospective data and no prospective data on their effect on transplantation outcomes are available. See panel 5 for recommendations on post-HCT evaluation and intervention.

Future research

Many questions regarding the role of MRD and MRD-guided interventions in the context of allo-HCT remain unresolved—further research is warranted. From a technical perspective, the development of increasingly sensitive methodologies, ideally applicable to peripheral blood samples, will deepen understanding of relapse biology and kinetics, including the mechanisms of immune escape. However, strategies improving the specificity of relapse prediction are equally crucial to ensure that potentially toxic interventions are administered only to patients who are likely to benefit, thereby avoiding unnecessary treatment in those at low risk of relapse. Such strategies might require the integration of complex data, including MRD, other biomarkers, molecular and cytogenetic profiles, and clinical variables, in a time-dependent and individualised

manner. In this context, single-cell analyses offer a promising avenue to elucidate clonal evolution after transplantation and might enhance the predictive value of MRD assessment. Advanced computational approaches, including artificial intelligence, are also expected to play a key role in supporting this complex decision making process.

Moreover, in the era of targeted and immunological therapies, the treatment landscape is evolving rapidly, with increasingly precise and less toxic options presenting a unique opportunity to improve the safety and effectiveness of transplantation. However, well designed studies are needed to define the role of these medications in realising deeper MRD-negative responses before HCT and their potential utility in post-transplantation maintenance and MRD-guided pre-emptive strategies.

Contributors

JS, GB, JE, MGD, MH, AN, GJR, MS, and FB: literature research, interpretation of data and the recommendations to be made, and preparation of figures. JS, GB, FC, FO, IS-O, IY-A, and FB: conceived and designed the manuscript topics to be covered. CC, RD, MH, and GJR reviewed the entire manuscript. All co-authors played an important role in interpreting results, revised the manuscript, approved the final version, and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All co-authors accept final responsibility for the decision to submit for publication.

Declaration of interests

GB: honoraria from Gilead, Jazz, and Medac; participation in advisory boards from BMS, Jazz, Novartis, and Sanofi; and travel support from Gilead, Jazz, and Sanofi. CC: honoraria and consulting fees from AbbVie, BMS, Astellas, and Daiichi Sankyo. RD: participation in advisory boards for AbbVie, BeiGene, Jazz, Menarini, Novartis, Pfizer, and Shattuck Labs; research grants from AbbVie and Amgen; speaker honoraria, consultancy, or educational events from AbbVie, Astellas, Jazz, Novartis, and Pfizer. JE: participation in advisory boards for AbbVie, Novartis, Astellas, Jazz Pharmaceuticals, BMS-Celgene, Pfizer, and Amgen; research funding to their institution from Novartis, Jazz Pharmaceuticals, and AbbVie; and Chair of the Molecular Markers Subcommittee of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation (EBMT). MH: research funding to their institution from: AbbVie, Bayer Pharma AG, Jazz Pharmaceuticals, Glycostem, Karyopharm, PinotBio, Servier, and Toray; honoraria from Astellas, Daiichi Sankyo, Janssen, Miltenyi, Otsuka, Qiagen, and Servier; and consultancy for AbbVie, AvenCell, Ascentage Pharma, Bristol Myers Squibb, Janssen, Jazz Pharmaceuticals, LabDelbert, Novartis, Pfizer, and Servier. DCdL: participation in company-sponsored speakers bureau for Roche Pharma, AbbVie, Servier, and Daiichi Sankyo; travel expenses from AbbVie; and scientific advisory board: Takeda, Servier, and Immedica Pharma. FO: lectures, speakers bureau, and educational events for Takeda; lectures and educational events for Kyowa Kirin; speakers bureau for Medac Pharma; travel expenses from Jazz Pharma and Kyowa Kirin; and Vice Chair of the Practice Harmonisation and Guidelines Committee of EBMT. GJR: consultancy for AbbVie, Amgen, AstraZeneca, Bristol Myers Squibb, Caribou Biosciences, Celgene, Daiichi Sankyo, Ellipses Pharma, Genoptix GlaxoSmithKline, Geron, Glycomimetics, Janssen, Jasper Pharmaceuticals, Jazz Pharmaceuticals, Molecular Partners, Morphosys, Neogenomics, Novartis, Oncoprecision, Oncotherapy, Pfizer, Rigel, Roche, and Syndax; and research support from Janssen. FB: consulting fees and participation in advisory boards for Jazz Pharmaceuticals, Laboratoires Delbert, and Novartis; and speaker for Astellas, Bristol Myers Squibb, Janssen-Cilag, and Servier. JS: Chair of the Alternative Donor Subcommittee of the Acute Leukemia Working Party of the EBMT. FC: Chair of the Acute Leukemia Working Party of the EBMT. AN: Chair of

Search strategy and selection criteria

An international panel of experts convened as part of the Acute Leukemia Working Party of the European Society for Blood and Marrow Transplantation and conducted a comprehensive review of the relevant literature available in the PubMed database. The search included articles in English published from database inception up to Jan 31, 2025, using combinations of the terms “acute myeloid leukemia”, “measurable residual disease”, “MRD”, “allogeneic transplant”, “maintenance therapy”, and “preemptive intervention”. Priority was given to clinical trials, consensus guidelines, meta-analyses, and high-impact peer-reviewed publications. Studies were selected based on their relevance to the transplantation setting, robustness of MRD detection methodology, and applicability to current clinical practice. Additional references were identified through manual searches of reference lists and expert recommendations from members of the EBMT Practice Harmonisation and Guidelines Committee. Ensuing an in-depth workshop, a draft of the recommendations was formulated and subsequently circulated to additional experts in the field for review and further contribution.

the Molecular Markers Subcommittee of the Acute Leukemia Working Party of the EBMT. AR: Vice Chair of the Practice Harmonisation and Guidelines Committee of EBMT, Chair of the Autoimmune Diseases Working Party of the EBMT, and Chair of the Cellular Therapy and Immunobiology Working Party of the EBMT. IS-O: Secretary of the Practice Harmonisation and Guidelines Committee of EBMT. IY-A: Vice Chair of the Practice Harmonisation and Guidelines Committee of EBMT. All other authors declare no competing interests.

References

- 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**: 2753–67.
- Döhner H, Wei AH, Appelbaum FR, et al. Diagnosis and management of AML in adults: 2022 recommendations from an international expert panel on behalf of the ELN. *Blood* 2022; **140**: 1345–77.
- 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**: 1890–99.
- Blachly JS, Walter RB, Hourigan CS. The present and future of measurable residual disease testing in acute myeloid leukemia. *Haematologica* 2022; **107**: 2810–22.
- Nagler A, Baron F, Labopin M, et al. Measurable residual disease (MRD) testing for acute leukemia in EBMT transplant centers: a survey on behalf of the ALWP of the EBMT. *Bone Marrow Transplant* 2021; **56**: 218–24.
- Wang Y, Chang YJ, Chen J, et al. Consensus on the monitoring, treatment, and prevention of leukaemia relapse after allogeneic hematopoietic stem cell transplantation in China: 2024 update. *Cancer Lett* 2024; **605**: 217264.
- Yakoub-Agha I, Greco R, Onida F, et al. Practice harmonization workshops of EBMT: an expert-based approach to generate practical and contemporary guidelines within the arena of hematopoietic cell transplantation and cellular therapy. *Bone Marrow Transplant* 2023; **58**: 696–700.
- Schuurhuis GJ, Heuser M, Freeman S, et al. Minimal/measurable residual disease in AML: a consensus document from the European LeukemiaNet MRD Working Party. *Blood* 2018; **131**: 1275–91.
- Grob T, Sanders MA, Vonk CM, et al. Prognostic value of *FLT3*-internal tandem duplication residual disease in acute myeloid leukemia. *J Clin Oncol* 2023; **41**: 756–65.
- Dillon LW, Gui G, Page KM, et al. DNA sequencing to detect residual disease in adults with acute myeloid leukemia prior to hematopoietic cell transplant. *JAMA* 2023; **329**: 745–55.
- Othman J, Potter N, Ivey A, et al. Postinduction molecular MRD identifies patients with NPM1 AML who benefit from allogeneic transplant in first remission. *Blood* 2024; **143**: 1931–36.
- Hourigan CS, Dillon LW, Gui G, et al. Impact of conditioning intensity of allogeneic transplantation for acute myeloid leukemia with genomic evidence of residual disease. *J Clin Oncol* 2020; **38**: 1273–83.
- Levis MJ, Hamadani M, Logan B, et al. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of *FLT3*. *J Clin Oncol* 2024; **42**: 1766–75.
- Wienecke CP, Heida B, Venturini L, et al. Clonal relapse dynamics in acute myeloid leukemia following allogeneic hematopoietic cell transplantation. *Blood* 2024; **144**: 296–307.
- Gronlund JK, Veigaard C, Juhl-Christensen C, Skou AS, Melsvik D, Ommen HB. Droplet digital PCR for sensitive relapse detection in acute myeloid leukaemia patients transplanted by reduced intensity conditioning. *Eur J Haematol* 2024; **112**: 601–10.
- Chen W, Huang J, Zhao Y, et al. Measurable residual disease monitoring by ddPCR in the early posttransplant period complements the traditional MFC method to predict relapse after HSCT in AML/MDS: a multicenter retrospective study. *J Transl Med* 2024; **22**: 410.
- Davis BH, Wood B, Oldaker T, Barnett D. Validation of cell-based fluorescence assays: practice guidelines from the ICSH and ICCS—part I—rationale and aims. *Cytometry B Clin Cytom* 2013; **84**: 282–85.
- Wood BL. Acute myeloid leukemia minimal residual disease detection: the difference from normal approach. *Curr Protoc Cytom* 2020; **93**: e73.
- Tettero JM, Freeman S, Buecklein V, et al. Technical aspects of flow cytometry-based measurable residual disease quantification in acute myeloid leukemia: experience of the European LeukemiaNet MRD Working Party. *HemaSphere* 2022; **6**: e676.
- Stelmach P, Trumpp A. Leukemic stem cells and therapy resistance in acute myeloid leukemia. *Haematologica* 2023; **108**: 353–66.
- Li SQ, Xu LP, Wang Y, et al. An LSC-based MRD assay to complement the traditional MFC method for prediction of AML relapse: a prospective study. *Blood* 2022; **140**: 516–20.
- Zeijlemaker W, Grob T, Meijer R, et al. CD34⁺CD38⁺ leukemic stem cell frequency to predict outcome in acute myeloid leukemia. *Leukemia* 2019; **33**: 1102–12.
- Blouin AG, Ye F, Williams J, Askar M. A practical guide to chimerism analysis: review of the literature and testing practices worldwide. *Hum Immunol* 2021; **82**: 838–49.
- Koreth J, Kim HT, Nikiforow S, et al. Donor chimerism early after reduced-intensity conditioning hematopoietic stem cell transplantation predicts relapse and survival. *Biol Blood Marrow Transplant* 2014; **20**: 1516–21.
- Ahci M, Stempelmann K, Buttkeireit U, et al. Clinical utility of quantitative PCR for chimerism and engraftment monitoring after allogeneic stem cell transplantation for hematologic malignancies. *Biol Blood Marrow Transplant* 2017; **23**: 1658–68.
- Klyuchnikov E, Badbaran A, Massoud R, et al. Post-transplantation day +100 minimal residual disease detection rather than mixed chimerism predicts relapses after allogeneic stem cell transplantation for intermediate-risk acute myelogenous leukemia patients undergoing transplantation in complete remission. *Transplant Cell Ther* 2022; **28**: 374.e1–9.
- Georgi JA, Stasik S, Bornhäuser M, Platzbecker U, Thiede C. Analysis of subset chimerism for MRD-detection and pre-emptive treatment in AML. *Front Oncol* 2022; **12**: 841608.
- Craddock C, Jackson A, Loke J, et al. Augmented reduced-intensity regimen does not improve post-allogeneic transplant outcomes in acute myeloid leukemia. *J Clin Oncol* 2021; **39**: 768–78.
- Freeman SD, Hills RK, Virgo P, et al. Measurable residual disease at induction redefines partial response in acute myeloid leukemia and stratifies outcomes in patients at standard risk without NPM1 mutations. *J Clin Oncol* 2018; **36**: 1486–97.
- Venditti A, Piciocchi A, Candoni A, et al. GIMEMA AML1310 trial of risk-adapted, MRD-directed therapy for young adults with newly diagnosed acute myeloid leukemia. *Blood* 2019; **134**: 935–45.
- Scott BL, Pasquini MC, Logan BR, et al. Myeloablative versus reduced-intensity hematopoietic cell transplantation for acute myeloid leukemia and myelodysplastic syndromes. *J Clin Oncol* 2017; **35**: 1154–61.
- Gilleece MH, Labopin M, Yakoub-Agha I, et al. Measurable residual disease, conditioning regimen intensity, and age predict outcome of allogeneic hematopoietic cell transplantation for acute myeloid leukemia in first remission: a registry analysis of 2292 patients by the Acute Leukemia Working Party European Society of Blood and Marrow Transplantation. *Am J Hematol* 2018; **93**: 1142–52.
- Eapen M, Rocha V, Sanz G, et al. Effect of graft source on unrelated donor haemopoietic stem-cell transplantation in adults with acute leukaemia: a retrospective analysis. *Lancet Oncol* 2010; **11**: 653–60.
- Horgan C, Mullanfroze K, Rauthan A, et al. T-cell replete cord transplants give superior outcomes in high-risk and relapsed/refractory pediatric myeloid malignancy. *Blood Adv* 2023; **7**: 2155–65.
- Sanz J, Labopin M, Choi G, et al. Younger unrelated donors may be preferable over HLA match in the PTcy era: a study from the ALWP of the EBMT. *Blood* 2024; **143**: 2534–43.
- Sanz J, Galimard JE, Labopin M, et al. Post-transplant cyclophosphamide after matched sibling, unrelated and haploidentical donor transplants in patients with acute myeloid leukemia: a comparative study of the ALWP EBMT. *J Hematol Oncol* 2020; **13**: 46.
- Milano F, Gooley T, Wood B, et al. Cord-blood transplantation in patients with minimal residual disease. *N Engl J Med* 2016; **375**: 944–53.

- 38 Chang YJ, Wang Y, Liu YR, et al. Haploidentical allograft is superior to matched sibling donor allograft in eradicating pre-transplantation minimal residual disease of AML patients as determined by multiparameter flow cytometry: a retrospective and prospective analysis. *J Hematol Oncol* 2017; **10**: 134.
- 39 Zhou Y, Othus M, Araki D, et al. Pre- and post-transplant quantification of measurable ('minimal') residual disease via multiparameter flow cytometry in adult acute myeloid leukemia. *Leukemia* 2016; **30**: 1456–64.
- 40 Walter RB, Buckley SA, Pagel JM, et al. Significance of minimal residual disease before myeloablative allogeneic hematopoietic cell transplantation for AML in first and second complete remission. *Blood* 2013; **122**: 1813–21.
- 41 Vlcárcel D, Martino R, Caballero D, et al. Sustained remissions of high-risk acute myeloid leukemia and myelodysplastic syndrome after reduced-intensity conditioning allogeneic hematopoietic transplantation: chronic graft-versus-host disease is the strongest factor improving survival. *J Clin Oncol* 2008; **26**: 577–84.
- 42 Lisak M, Nicklasson M, Palmason R, et al. Higher cyclosporine-A concentration increases the risk of relapse in AML following allogeneic stem cell transplantation from unrelated donors using anti-thymocyte globulin. *Sci Rep* 2023; **13**: 22777.
- 43 Sharma N, Zhao Q, Ni B, et al. Effect of early post-transplantation tacrolimus concentration on the risk of acute graft-versus-host disease in allogeneic stem cell transplantation. *Cancers* 2021; **13**: 613.
- 44 Klyuchnikov E, Badbaran A, Massoud R, et al. Enhanced immune reconstitution of $\gamma\delta$ T cells after allogeneic stem cell transplantation overcomes the negative impact of pretransplantation minimal residual disease-positive status in patients with acute myelogenous leukemia. *Transplant Cell Ther* 2021; **27**: 841–50.
- 45 Pagliuca S, Schmid C, Santoro N, et al. Donor lymphocyte infusion after allogeneic haematopoietic cell transplantation for haematological malignancies: basic considerations and best practice recommendations from the EBMT. *Lancet Haematol* 2024; **11**: e448–58.
- 46 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**: 215–23.
- 47 Stadler M, Hambach L, Dammann E, et al. The graft-versus-leukemia effect of prophylactic donor lymphocyte infusions after allogeneic stem cell transplantation is equally effective in relapse prevention but safer compared to spontaneous graft-versus-host disease. *Ann Hematol* 2023; **102**: 2529–42.
- 48 Yan CH, Liu DH, Liu KY, et al. Risk stratification-directed donor lymphocyte infusion could reduce relapse of standard-risk acute leukemia patients after allogeneic hematopoietic stem cell transplantation. *Blood* 2012; **119**: 3256–62.
- 49 Greiner J, Götz M, Bunjes D, Hofmann S, Wais V. Immunological and clinical impact of manipulated and unmanipulated DLI after allogeneic stem cell transplantation of AML patients. *J Clin Med* 2020; **9**: 39.
- 50 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**: 1201–12.
- 51 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**: 2993–3002.
- 52 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**: 5580–88.
- 53 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**: 5857–65.
- 54 Fathi AT, Kim HT, Soiffer RJ, et al. Multicenter phase I trial of ivosidenib as maintenance treatment following allogeneic hematopoietic cell transplantation for IDH1-mutated acute myeloid leukemia. *Clin Cancer Res* 2023; **29**: 2034–42.
- 55 Garcia JS, Kim HT, Murdock HM, et al. Prophylactic maintenance with venetoclax/azacitidine after reduced-intensity conditioning allogeneic transplant for high-risk MDS and AML. *Blood Adv* 2024; **8**: 978–90.
- 56 Platzbecker U, Middeke JM, Sockel K, et al. Measurable residual disease-guided treatment with azacitidine to prevent haematological relapse in patients with myelodysplastic syndrome and acute myeloid leukaemia (RELAZA2): an open-label, multicentre, phase 2 trial. *Lancet Oncol* 2018; **19**: 1668–79.
- 57 Huang C, Jia Y, Yang J, et al. Azacitidine combined with interferon- α for pre-emptive treatment of AML/MDS after allogeneic peripheral blood stem cell transplantation: a prospective phase II study. *Br J Haematol* 2024; **205**: 1067–76.
- 58 Metzelder SK, Schroeder T, Lübbert M, et al. Long-term survival of sorafenib-treated FLT3-ITD-positive acute myeloid leukaemia patients relapsing after allogeneic stem cell transplantation. *Eur J Cancer* 2017; **86**: 233–39.
- 59 Mathew NR, Baumgartner F, Braun L, et al. Sorafenib promotes graft-versus-leukemia activity in mice and humans through IL-15 production in FLT3-ITD-mutant leukemia cells. *Nat Med* 2018; **24**: 282–91.
- 60 Tiong IS, Hiwase DK, Abro E, et al. Targeting molecular measurable residual disease and low-blast relapse in AML with venetoclax and low-dose cytarabine: a prospective phase II study (VALDAC). *J Clin Oncol* 2024; **42**: 2161–73.
- 61 Jimenez-Chillon C, Othman J, Taussig D, et al. Venetoclax-based low intensity therapy in molecular failure of NPM1-mutated AML. *Blood Adv* 2024; **8**: 343–52.
- 62 Issa GC, Aldoss I, DiPersio J, et al. The menin inhibitor revumenib in KMT2A-rearranged or NPM1-mutant leukaemia. *Nature* 2023; **615**: 920–24.
- 63 Erba HP, Fathi AT, Issa GC, et al. Update on a phase 1/2 first-in-human study of the menin-KMT2A (MLL) inhibitor ziftomenib (KO-539) in patients with relapsed or refractory acute myeloid leukemia. *Blood* 2022; **140** (suppl 1): 153–56.
- 64 Balsat M, Renneville A, Thomas X, et al. Postinduction minimal residual disease predicts outcome and benefit from allogeneic stem cell transplantation in acute myeloid leukemia with NPM1 mutation: a study by the Acute Leukemia French Association Group. *J Clin Oncol* 2017; **35**: 185–93.
- 65 Pratz KW, Jonas BA, Pullarkat V, et al. Measurable residual disease response and prognosis in treatment-naïve acute myeloid leukemia with venetoclax and azacitidine. *J Clin Oncol* 2022; **40**: 855–65.
- 66 Pratz KW, Jonas BA, Pullarkat V, et al. Long-term follow-up of VIALE-A: venetoclax and azacitidine in chemotherapy-ineligible untreated acute myeloid leukemia. *Am J Hematol* 2024; **99**: 615–24.
- 67 Thol F, Gabdoulline R, Liebig A, et al. Measurable residual disease monitoring by NGS before allogeneic hematopoietic cell transplantation in AML. *Blood* 2018; **132**: 1703–13.
- 68 Dillon R, Hills R, Freeman S, et al. Molecular MRD status and outcome after transplantation in NPM1-mutated AML. *Blood* 2020; **135**: 680–88.
- 69 Fraccaroli A, Jurinovic V, Hirschbühl K, et al. Pre-transplant MRD does not seem to impact survival in NPM1-mutated AML undergoing allogeneic stem cell transplantation. *Blood Adv* 2025; **9**: 1630–41.
- 70 Craddock C. Transplant in AML with measurable residual disease: proceed or defer? *Hematology Am Soc Hematol Educ Program* 2022; **2022**: 528–33.
- 71 Shah MV, Jorgensen JL, Saliba RM, et al. Early post-transplant minimal residual disease assessment improves risk stratification in acute myeloid leukemia. *Biol Blood Marrow Transplant* 2018; **24**: 1514–20.
- 72 McCarthy N, Gui G, Dumezy F, et al. Pre-emptive detection and evolution of relapse in acute myeloid leukemia by flow cytometric measurable residual disease surveillance. *Leukemia* 2024; **38**: 1667–73.
- 73 Radich J. Transplant, MRD, and predicting relapse in AML. *Blood* 2024; **144**: 245–47.

Copyright © 2025 Elsevier Ltd. All rights reserved, including those for text and data mining, AI training, and similar technologies.