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REVIEW

Strategies to reduce relapse risk in patients undergoing allogeneic stem cell transplantation for acute myeloid leukaemia

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Summary
Allogeneic stem cell transplantation is a centrally important curative strategy in adults with acute myeloid leukaemia; however, relapse occurs in a significant proportion of patients and remains the leading cause of treatment failure. The prognosis for patients who relapse post-transplant remains poor, and the development of new strategies with the ability to reduce disease recurrence without increasing transplant toxicity remains a priority. In this review, within the context of our understanding of disease biology and the graft-versus-leukaemia (GVL) effect, we will discuss established, evolving and novel approaches for increasing remission rates, decreasing measurable residual disease pretransplant, future methods to augment the GVL effect and the opportunities for post-transplant maintenance. Future progress depends upon the development of innovative trials and networks, which will ensure the rapid assessment of emerging therapies in prospective clinical trials.

KEYWORDS
acute myeloid leukaemia, Allo-SCT, relapse

INTRODUCTION

Notwithstanding the development of novel therapies and advances in supportive care, the majority of fit adults with newly diagnosed acute myeloid leukaemia (AML) in 2024 are still destined to die of relapsed or refractory disease. A potent graft-versus-leukaemia (GVL) effect coupled with the development of reduced intensity conditioning (RIC) regimens, and increased donor availability, has resulted in allogeneic stem cell transplantation (allo-SCT) becoming a core component of the treatment algorithm for fit adults up to the age of 75 with AML.[1–3] While the advances in supportive care and improvements in GVHD prophylaxis have substantially reduced the toxicity of allo-SCT,[4] there has been only modest progress in reducing the risk of disease relapse which continues to be the major cause of transplant failure.[5–7]

Therapeutic interventions with the potential to reduce the risk of disease relapse post-transplant are therefore urgently needed, and their design is underpinned by both our evolving understanding of the biology of disease relapse and the characterisation of tractable factors determining relapse risk.[8–12]

BIOLOGY OF AML AND DISEASE RELAPSE

Disease biology is a major risk factor for post-transplant relapse and both the presence of a complex karyotype and mutations in genes including *TP53* and *FLT3-ITD* are associated with an increased risk of relapse.[10,13,14] Additional important determinants of post-transplant relapse include conditioning regimen intensity and pretransplant disease status including measurable residual disease (MRD) levels[15–18]

Clonal evolution is increasingly recognised as an important characteristic of post-transplant relapse. This can result in acquired loss of potentially targetable mutations and

has implications for the choice of maintenance strategies.[19] Notably though, the greatest transcriptional change in relapsed AML post allo-SCT is not related to differences in the spectrum of lost or gained mutations but is rather directed towards mechanisms promoting the immune evasion of the GVL effect.[20] The best described mechanism is reduced HLA expression with the loss of the mismatched HLA haplotype after haploidentical transplantation,[8,12,21,22] and the downregulation of HLA Class II after HLA-matched transplantation.[23]

In addition to the clonal loss of targetable antigens and mechanisms of antigen presentation, the modulation of the GVL effect by the disease microenvironment may be an important mechanism of disease relapse following allo-SCT. In *TP53*-mutated AML, the native immune signature appears suppressive, characterised by increased PD-L1 expression, reduced numbers of bone marrow infiltrating cytotoxic T and NK cells, and increased proportions of regulatory T cells (Tregs).[13]

Accordingly, immune prognostic modelling in patients with high-risk AML independently predicts survival in patients, where high-risk disease is characterised by greater proportions of $CD8^+$ T cells, Tregs and increased expression of checkpoint blockade molecules.[24] Given that the immune profile determines clinical response to therapies in bone marrow failure syndromes,[25] it is feasible that the immune profile of AML modulates native or allogeneic cytotoxic immune responses, leading to increased relapse rates post-transplant for patients with high-risk AML.[26] Consistent with this hypothesis, leukaemic blasts in patients who relapse demonstrate increased expression of checkpoint blockade ligands, with corresponding checkpoint molecules such as PD-1, KLRG-1 and TIGIT found on AML-specific T cells.[27,28] In particular, a PD-1+ TIM-3+ KLRG1+ 2B4+ profile typifies functionally 'exhausted' $CD8^+$ stem-like memory T cells, found in the bone marrow of AML patients at relapse.[29] While this appeared to be characteristic in recipients of haploidentical and unrelated transplants, it is less so for recipients of cord blood transplants.[30]

Overall, this increased understanding of the biology of AML and disease relapse post allograft is yet to translate into established preventative therapies, but it is hoped that the knowledge will inform the design of future pre-, peri- and post-transplant strategies to mitigate against it (Figure 1).

PRETRANSPLANT TREATMENT STRATEGIES TO REDUCE DISEASE RELAPSE FOLLOWING allo-SCT

MRD status provides a dynamic risk assessment of disease response to treatment, and pretransplant MRD status is an important prognostic factor of relapse following allo-SCT. A number of methodologies exist to assess MRD prior to transplant: PCR monitoring of appropriate molecular markers such as *NPM1* offers a sensitive approach,[31] while multiparameter flow cytometry (MFC) provides a widely applicable method for patients without a molecular marker.[17,32] These studies almost uniformly demonstrate an increased risk of relapse in patients with detectable MRD prior to allo-SCT, and the significance of pretransplant MRD has been further confirmed in two recent prospective studies.[18,33] Not

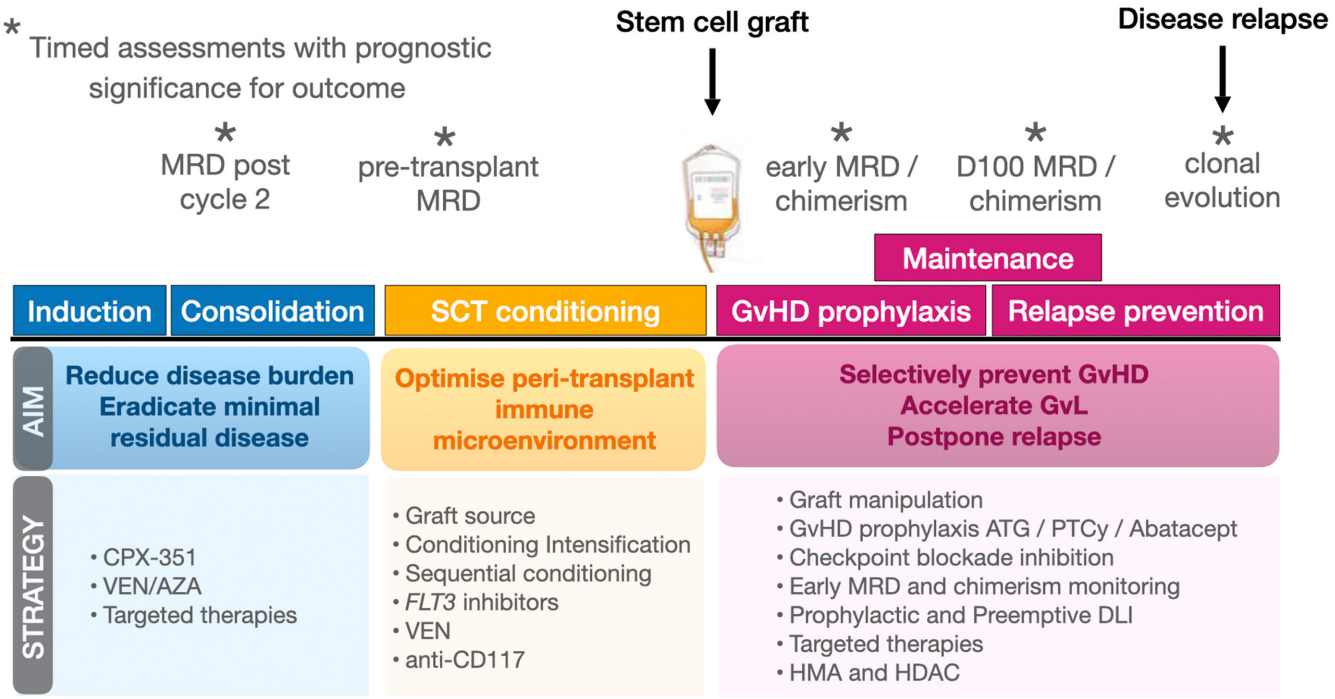

FIGURE 1 Strategies to decrease disease relapse in patients undergoing allogeneic stem cell transplantation for AML. AML, acute myeloid leukaemia; AZA, azacitidine; GVL, graft-versus-leukaemia; MDS, myelodysplastic syndrome; MRD, measurable residual disease; SCT, stem cell transplantation; VEN, venetoclax.

only did these confirm the prognostic value of pretransplant MRD but they also provided insights into the underlying biology of MRD, alongside possible means by which MRD may be manipulated.

Pretransplant-targeted therapy can modify MRD in patients undergoing allo-SCT for *FLT3*-mutated AML, where the addition of midostaurin to induction chemotherapy improved overall survival, particularly those who achieved first complete remission (CR1) and underwent allo-SCT.[11] Similarly, the QuANTUM-First trial demonstrated that the post-transplant survival benefit conferred by quizartinib was most marked in patients who were MRD positive prior to allo-SCT.[34]

Historic registry data did not demonstrate a significant benefit to additional cycles of intensive chemotherapy prior to allo-SCT, but more recently improved post-transplant outcomes have been observed in patients with secondary AML who received induction CPX-351 as compared to conventional DA (7 + 3).[35–37] In the phase III prospective study, CPX-351 had a similar safety profile compared to DA (7 + 3),[37] whereas in the AML19 trial which compared CPX-351 with FLAG-IDA in younger adults with newly diagnosed adverse cytogenetic AML or high-risk myelodysplastic syndromes (MDSs) a post-transplant survival benefit was only observed in patients with MDS-related mutations,[38] suggesting overall that benefit from augmented induction chemotherapy may be restricted to patients with high-risk AML.

Landmark studies have demonstrated that the BCL2 inhibitor venetoclax (VEN) in combination with azacitidine (AZA) improves CR/complete remission with incomplete count recovery rates compared to AZA alone in patients over the age of 75 unfit for intensive chemotherapy.[9] A significant number of patients treated with VEN/AZA also achieve an MRD-negative CR,[39] where it appears to be particularly effective in the treatment of *NPM1*-mutated AML. Preliminary data are emerging to suggest that it may be able to overcome overt *NPM1* relapse in fit adults, and induce deep remissions, which would permit subsequent allo-SCT.[40] VEN/AZA is also being explored in combination with *FLT3* inhibitors such as gilteritinib and quizartinib, where retrospective and prospective phase I/II data demonstrate high CR rates with an encouraging levels of MRD negativity in older patients with *FLT3* mutated AML unfit for intensive chemotherapy.[41–44] Retrospective data support the concept that VEN/AZA may be utilised successfully as a bridge to allo-SCT,[45] where short-term post-transplant outcomes appear similar to those seen following induction with intensive chemotherapy[46,47] in patients over the age of 60 with newly diagnosed AML. Separately, a number of groups have reported high CR rates and impressive MRD clearance when VEN is combined with intensive chemotherapy regimens such as DA or FLAG-IDA, highlighting an opportunity to optimise conventional induction chemotherapy strategies prior to transplant.[48,49] Prospective validation of these approaches is required to understand post-transplant outcomes of patients treated with VEN/AZA as compared to traditional induction chemotherapy regimens in fit adults, but this is currently under investigation in an important randomised study (NCT04801797) within US centres.

Overall, the impact of combination pretransplant therapy on longer term survival remains unclear, and further follow-up data are required to better understand this. Future randomised trials will be required to address whether additional therapy prior to transplant improves the outcome for patients with intermediate risk disease, as well as high-risk patients. Other important questions will include accurately identifying patients without an MRD marker who might benefit from additional pretransplant therapy or post-transplant maintenance treatment, and the role of allo-SCT in patients with intermediate risk AML who derive survival benefit from combination pretransplant strategies.

THE IMPACT OF GRAFT SOURCE AND CONTENTS ON RELAPSE FOLLOWING allo-SCT

The expansion of international donor registries has increased donor options for patients without a matched sibling donor. Equivalent clinical outcomes are observed in patients undergoing allo-SCT with well-matched (8/8 or 10/10) volunteer unrelated donors as compared to matched sibling donors,[50–52] and the refinement of HLA molecular matching has improved our understanding of the potential clinical benefit of HLA-DPB1 'permissive mismatching', with the aim of augmenting a GVL effect without increasing the risk of GVHD.[53,54]

Several retrospective studies have assessed the impact of T-cell depletion (TCD) as GVHD prophylaxis on the risk of AML relapse post allo-SCT using matched sibling or unrelated donors. A large registry analysis found that ATG did not increase relapse rates in AML patients irrespective of their MRD status pretransplant.[55] Similarly, the use of in vivo alemtuzumab in the setting of RIC was not found to be an independent risk factor for relapse, whereas high levels of post-transplant ciclosporin was.[1] In the myeloablative setting, the use of ex vivo TCD with CD34-selected grafts did not increase the risk of relapse in patients undergoing allo-SCT in CR1, but those with high-risk features had significantly poorer outcomes.[56] More recently, prospective trials have demonstrated that the use of ATG or abatacept as in vivo TCD can ameliorate severe GVHD while not detrimentally increasing relapse rates.[57,58] The advent of post-transplant cyclophosphamide (PTCY) as an effective method of GVHD prophylaxis[59] has led to significant improvements in the outcomes of patients with high-risk AML transplanted using haploidentical donors.[60,61] Registry data suggest that haploidentical allo-SCT with PTCY may even overcome the poor prognosis of secondary AML, as comparable relapse rates were observed in this cohort compared to patients undergoing haploidentical allo-SCT for de novo AML.[62] Rates of disease relapse are also similar to those of PTCY compared to T-replete calcineurin-based GVHD prophylaxis in patients undergoing allo-SCT with matched unrelated donors.[63] For the majority of paediatric patients,

a haploidentical donor is most likely to be either the child's mother or father. Exposure of the patient to non-inherited maternal antigen (NIMA) may enhance the GVL effect, and decreased relapse (and non-relapse) mortality has been observed with maternal rather than paternal haploidentical donors.[64] For adult patients, siblings and children may be considered, and in the setting of T-replete haplo-SCT with PTCY, these are preferred to a parental donor, but the impact of NIMA or non-inherited paternal antigen (NIPA) mismatching on outcome remains unclear, and fathers are the preferred parental donor.[65,66]

Similarly, the expansion of umbilical cord registries, and the recent demonstration of a potent GVL effect in umbilical cord allo-SCT for paediatric myeloid diseases using a T-replete umbilical cord transplant platform,[67] has expanded the potential pool of alternative donors for patients with high-risk AML. The BMT CTN 1101 trial[68] reported equivalent relapse rates for adult patients undergoing allo-SCT with haploidentical or umbilical cord grafts, but this trial was not specific to AML and employed conditioning regimens not currently used. In this context, retrospective datasets demonstrating a lower relapse rate in patients with AML in CR1, and the importance of pretransplant MRD after a cord blood transplant, justify a future randomised trial.[67,69] While more data are therefore required to determine a preference in alternative donor source in relation to disease relapse AML prevention, the increased availability of alternative options for patients lacking a matched sibling or 10/10 (8/8) unrelated donor is of great practical importance and means that most eligible patients can be now considered for allo-SCT.

There is increasing interest in the impact of graft-derived effector cells on relapse risk following allo-SCT, and a high dose of NK cells within the stem cell graft has been found to significantly reduce relapse rates in patients undergoing transplant with matched sibling or matched unrelated donors.[70] The optimisation of T cell-depleting strategies and stem cell bag composition may therefore have the potential to improve both relapse and non-relapse mortality post allo-SCT for AML.

OPTIMISING THE CONDITIONING REGIMEN TO PREVENT DISEASE RELAPSE

The important question concerning the choice of a myeloablative (MAC) or RIC regimen in patients undergoing allo-SCT for AML in CR1 was addressed by the BMT-CTN 0901 trial. In this study, both event-free and overall survival were improved in patients receiving a MAC regimen, although questions remain concerning the unusually low relapse rates in patients allocated to a MAC regimen and the high relapse rate observed in the RIC arm of this study.[16,71] Importantly, patients with detectable pretransplant MRD demonstrated markedly improved survival after a MAC regimen compared with the recipients of a RIC regimen; a benefit not observed in patients who were MRD negative pretransplant.[18] It therefore seems reasonable to choose a MAC regimen in younger fit patients in CR1, especially if there is detectable MRD pretransplant. However, it remains unclear as to what represents the optimal conditioning regimen for the majority of patients who are not able to tolerate a MAC regimen.[72] A number of fludarabine-based RIC regimens are in common use including fludarabine with busulfan (FB2) and with melphalan (FM). More recently fludarabine/treosulfan regimens have been studied and are well tolerated with superior outcomes being demonstrated in one study.[73]

A 'sequential approach' in which additional chemotherapy is delivered prior to a standard RIC allo-SCT has also been explored.[74–76] Malard et al. retrospectively studied the impact of additional chemotherapy with the FLAMSA-BU schedule (fludarabine, amsacrine, cytarabine and busulfan) and reported reduced disease relapse in high-risk AML in a registry-based analysis.[77] The UK FIGARO study randomised patients to either a standard RIC regimen or a FLAMSA-BU sequential regimen but was unable to demonstrate a survival advantage even in patients with detectable pretransplant MRD.[33] The development of innovative and tolerable RIC regimens which provide a lower risk of disease relapse therefore remains a priority, and the COSI trial, now fully recruited, is addressing the question of whether incorporation of thiotepa into a FB2-based regimen improves transplant outcomes.

The augmentation of transplant conditioning regimens with targeted therapies is an important emerging area of interest. The addition of VEN to MAC or RIC transplant platforms appears safe, with no detrimental impact on engraftment, and encouraging early phase data.[78,79] The adjunctive use of sorafenib, a *FLT3* tyrosine kinase inhibitor, in combination with fractionated myeloablative conditioning, has been shown to be tolerable in patients allografted for *FLT3-ITD*-mutated AML.[80] In the non-myeloablative setting, the addition of the CD117-targeting monoclonal antibody JSP191 appears safe, resulting in high levels of donor stem cell engraftment,[81] while in patients with relapsed or refractory AML the ongoing SIERRA trial is examining the use of an I-labelled anti-CD45 monoclonal antibody in conjunction with a non-myeloablative fludarabine/low-dose TBI conditioning regimen.[82] Overall, these studies demonstrate the feasibility of delivering combination therapy within conditioning regimens but larger prospective trials with longer follow-up will be required to change current practice.

OPPORTUNITIES TO OPTIMISE A GVL EFFECT POST-TRANSPLANT

The classical allogeneic immune response post-transplant is mediated by donor T cells[83] and advances in immunobiology have led to the development of a range of therapeutic targets for disease relapse prevention. Evidence for the importance of an early allogeneic immune response not only comes from the established correlation between the intensity

of post-transplant immunosuppression and relapse risk[1,84] but is also supported by the observation that persistence of disease associated mutations 30 days post-transplant in patients undergoing allo-SCT for myelodysplasia correlated with an increased risk of disease relapse.[85] Similarly, it has been demonstrated in several retrospective and prospective studies that very early acquisition of full donor chimerism appears to be protective against relapse in various myeloid disorders.[86–88] Early mixed chimerism, sustained by both patient and donor-derived Tregs suppresses the allogeneic immune response, reducing the risk of GVHD but increasing relapse.[89] In contrast, early infusion of donor-derived Tregs appears to be effective in limiting graft-versus-host disease, without increasing disease relapse.[90,91]

A relapse-associated gene signature has been described in donor $CD8^+$ T cells as early as 14 days post in vivo T cell-depleted allo-SCT, where the high expression of the checkpoint molecule CD94 (NKG2A) and low expression of the activator molecule CD96 (TACTILE) on $CD8^+$ T cells is associated with a 4.7-fold and 2.2-fold increased risk of relapse respectively.[92] CD94 is routinely expressed by NK cells, activated αβ $CD8^+$ T cells, γδ-T cells and NK T cells, and monalizumab is a non-depleting, blocking monoclonal antibody specific to the CD94/NKG2A receptor. A phase I study has suggested that monalizumab is safe 2 months post allo-HSCT,[93] and the results of an ongoing phase II study are awaited. This trial was proposed on the basis that CD94 (NKG2A) is classically thought of as a NK cell checkpoint axis, that NK cells are the predominant reconstituting lymphocyte within the first few weeks following allo-SCT, and that the induction of dysfunctional NK cells is well recognised in AML.[94] Leukaemic stem cells also have decreased expression of NKG2D ligands,[95] and relapse post allo-SCT is associated with reduced NK cell targets, as well as HLA.[8,12,20] In addition to the CD94 axis, $CD70^+$ $CD8^+$ T cells, detectable 14 days post allo-SCT, have been found to be allo-reactive memory T cells which track into tissues and cause acute GVHD.[96,97] CD70 is also expressed by AML blasts[98] such that it may represent an ideal target for the early prevention of both GVHD and disease relapse. The CD70-targeting monoclonal antibody cusatuzumab has been shown to be safe and have encouraging anti-leukaemic efficacy in AML in early phase trials.[98]

This improved understanding of the immune mechanisms underlying the GVL effect has led to a series of immune approaches to augment the allogeneic immune response. These would ideally target leukaemia-specific antigens resulting from AML-specific mutations. While some translocations (*AML1-ETO*, *PML-RARA* and *BCR-ABL*) and gain-of-function mutations (*FLT3-ITD*, *NPM1* and *IDH1/2*) give rise to such antigens,[99] AML is a cancer with one of the lowest mutational burdens.[100] Lineage-restricted antigens in AML include CD33, CD123 and NKGD2[99]; however, sharing of these epitopes with healthy tissue increases the potential damage elicited by targeted immunotherapies. Consequently, there is interest in pharmacological as well as cellular strategies for improving transplant outcome.

PHARMACOLOGICAL MAINTENANCE STRATEGIES FOLLOWING allo-SCT

Post-transplant maintenance therapy is emerging as an important manoeuvre to reduce the risk of disease relapse post transplant. It has the potential to reduce relapse either by targeting residual leukaemia, buying time for the genesis of a clinically significant GVL effect, or, alternatively, by augmenting the alloreactive response. Hypomethylating agents such as AZA and decitabine are attractive in this setting as they have inherent anti-leukaemic activity and up-regulate the expression of both epigenetically silenced minor histocompatibility antigens and putative tumour antigens, such as cancer testis antigens.[101,102] A number of retrospective studies have demonstrated that both agents are well tolerated post-transplant, albeit using an attenuated dosing schedule. A recent prospective randomised study[103] failed to show a survival benefit using post-transplant AZA when administered subcutaneously, although the duration of administration in many patients was short. The results of the UK-based, randomised AMADEUS trial, which utilised the well-tolerated oral preparation of AZA (CC486), are awaited, and may help to identify the best schedule for treatment.

Patients undergoing allo-SCT for *FLT3*-mutated AML may be a group whose outcomes are particularly improved by post-transplant maintenance therapy. They have a rapid relapse trajectory, and a number of novel *FLT3* inhibitors have shown promise as post-transplant maintenance.[104] Two randomised trials have demonstrated a survival benefit using post-transplant maintenance with sorafenib,[105,106] and the final peer-reviewed results of the MORPHO (BMT-CTN 1506) trial which examined the use of gilteritinib in this setting are imminently awaited. Data presented from this trial in abstract form showed improvement in relapse-free survival specifically in patients with detectable MRD going into transplant.[107] Pharmacological maintenance strategies are also being explored using the *IDH1* inhibitor enasidenib, and post-transplant maintenance with menin inhibitors is also an area of growing interest. Prospective studies in this area should aim to determine the prognostic value of MRD before and after allo-SCT, the identification of patients who would benefit from maintenance therapy in the absence of molecular disease markers, the impact of maintenance strategies on later complications such as GVHD and when maintenance therapy might reasonably be discontinued. Table 1 outlines the ongoing phase II and III trials of post-transplant pharmacological maintenance therapies to prevent disease relapse.

CELLULAR THERAPY STRATEGIES FOLLOWING allo-SCT

Donor lymphocyte infusions (DLIs) are an established cellular strategy for preventing AML relapse following allo-SCT, and are commonly administered prophylactically in patients

TABLE 1 Ongoing prospective phase II and III trials investigating pharmacological post-transplant maintenance therapies in the prevention of disease relapse.

Study ID	Intervention	Schedule	Design	Patient population	Status
NCT04809181	VEN/AZA	Unknown	Phase II	AML/MDS patients with detectable MRD post transplant	Recruiting
NCT04128501	VEN/AZA	AZA SC Days 1–5 if MRD negative or 1–7 if positive and VEN QD Days 1–7 if MRD negative or 1–14 if positive	Phase II	High-risk AML patients after allo-SCT	Recruiting
NCT03286530	Ruxolitinib	28-day cycle of twice daily fixed dose	Phase II	AML in CR1 undergoing RIC allo-SCT	Recruiting
NCT05429632	Mocravimod	28-day cycle of either 3 mg or 1 mg orally OD versus placebo	Phase III	High-risk or intermediate-risk AML patients in CR1 or any risk in CR2 undergoing allo-SCT	Recruiting
NCT04161885	VEN/AZA	28-day cycle of venetoclax 200 mg OD and AZA 20 mg/m^2 Days 1–5 versus best supportive care	Phase III	AML patients with <10% blasts before transplant and less than 5% blasts after transplant	Active, not recruiting
NCT04173533	CC-486	28-day cycle of oral AZA 200 mg OD Days 1–14 versus placebo	Phase III	AML/high-risk MDS/CMML CPSS int-2 or high risk in remission at the time of transplant and at the time of the enrolment	Active, not recruiting

Abbreviations: AML, acute myeloid leukaemia; AZA, azacitidine; CMML, chronic myelomonocytic leukaemia; CPSS, CMML-specific prognostic scoring system; MDS, myelodysplastic syndrome; MRD, measurable residual disease; SCT, stem cell transplantation; VEN, venetoclax.

with high-risk AML. While retrospective studies vary in the timing and dosing of prophylactic DLI, benefit is implied by increased post-transplant overall survival, particularly in high-risk and relapsed/refractory AML.[108–112] This extends into the haploidentical transplant setting but with an accompanying 33% rate of DLI-induced GVHD.[113] Most data in support of prophylactic DLI are retrospective, so the results of the UK-based prospective randomised PRO-DLI study (NCT02856464) are eagerly awaited and may change practice.

Pre-emptive DLI is used to prevent impending relapse heralded by either a loss of complete donor chimerism or the detection of MRD. Evidence is predominantly retrospective, but a large prospective study in various haematological malignancies demonstrated a significant reduction in the incidence of disease relapse.[114] This was confirmed specifically for AML in two studies in which pre-emptive DLI was triggered by both mixed chimerism[115] and MRD.[116]

The potential benefit of prophylactic and pre-emptive DLI must be considered in the light of the attendant toxicities, namely GVHD, where the rates of acute and chronic GVHD are approximately 12% and 31% respectively.[110]

Approaches to modify the cellular composition of DLI in order to increase itss efficacy and decrease the risk of GVHD have included Treg depletion,[117,118] memory T-cell enrichment,[119] ex vivo activation, or cytokine induction of DLI preinfusion,[120,121] and combination with other targeted therapies such as sorafenib[122] and VEN.[123]

Future prospective studies of pre-emptive DLI would benefit from a harmonisation of methods and standards for post-transplant MRD and chimerism monitoring, and are likely to require collaborative networks to recruit meaningful patient numbers. The realisation of genetic and cellular engineering also promises exciting new cell therapies to modulate or recapitulate the GVL response, but these are not yet readily deployable.

CONCLUSION

Disease relapse remains the dominant cause of treatment failure in patients allografted for AML. Developments in induction chemotherapy options coupled with the therapeutic approaches to target pretransplant MRD have the potential to reduce the risk of post-transplant relapse. Nevertheless, there remains an important opportunity to improve the anti-leukaemic activity of the conditioning regimen without an attendant increase in toxicity using new drugs or radiolabelled antibodies. Finally, perhaps the most promising approach is the development of new drug or cellular interventions post-transplant with the aim of maximising a GVL effect. If patients are to benefit from these exciting therapeutic options, it is increasingly clear that the accelerated delivery of high-quality randomised trials with embedded MRD and genomic data will be required, and trial acceleration models such as the US BMT CTN and the UK IMPACT transplant trial network will be increasingly important.[124]

AUTHOR CONTRIBUTIONS

FK and CC conceptualised the review. FK organised its content and wrote the initial draft. All authors contributed to the intellectual input and worked on subsequent revisions, and approved the final submitted manuscript.

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