



Prevention and management of relapse after allogeneic hematopoietic cell transplantation in hematological malignancies

# Relapse after allogeneic hematopoietic stem cell transplantation in acute myeloid leukemia: an overview of prevention and treatment

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## Abstract

Despite therapeutic progress in acute myeloid leukemia (AML), relapse post-allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a major challenge. Here, we aim to provide an overview of prevention and treatment of relapse in this population, including cell-based and pharmacologic options. Post-transplant maintenance therapy is used in patients who have undetectable measurable residual disease (MRD), while pre-emptive treatment is administered upon detection of MRD. Prompt transfusion of prophylactic donor lymphocyte infusion (DLI) was found to be effective in preventing relapse and overcoming the negative impact of detectable MRD. In addition, patients with persistent targetable mutations can benefit from targeted post-transplant pharmacological interventions. IDH inhibitors have shown promising results in relapsed/refractory AML. Hypomethylating agents, such as decitabine and azacitidine, have been studied in the post-allo-HSCT setting, both as pre-emptive and prophylactic. Venetoclax has been shown effective in combination with hypomethylating agents or low-dose cytarabine in patients with newly diagnosed AML, especially those unfit for intensive chemotherapy. FLT3 inhibitors, the topic of another section in this review series, have significantly improved survival in FLT-3-ITD mutant AML. The role of other cell-based therapies, including CAR-T cells, in AML is currently being investigated.

**Keywords** AML · Leukemia · Allogeneic stem cell transplantation · Transplantation relapse · Azacitidine · Sorafenib

## Introduction

Allogeneic hematopoietic stem cell transplantation (allo-HSCT) constitutes an important therapeutic option for patients with acute myeloid leukemia (AML), the most common indication for transplant. Allo-HSCT provides the highest potential for long-term survival in both settings, post-first remission and salvage post-relapse [1, 2]. However, despite improvement in treatment regimens, relapse post-allo-HSCT remains a major cause of treatment failure with up to half

of AML patients sustaining relapse, depending on the disease characteristics, and the type of conditioning regimen used. Moreover, the 2-year overall survival (OS) for AML patients who relapse after allo-HSCT remains low, reported to be less than 20% despite modest improvement in younger adults in recent years [2–5]. This adds to the challenge of treatment of AML, especially that a significant proportion of patients who have early relapse may either not tolerate or be refractory to intensive therapy after the toxicity of the prior transplant [4].

Several factors have been associated with a higher risk of post-transplant relapse. These include absence of complete hematologic remission at the time of transplantation, high-risk cytogenetic characteristics, T-cell depletion, and the use of reduced intensity conditioning (RIC) regimens [5–7]. Advancement in molecular techniques over the past decade, particularly next-generation-sequencing (NGS), has been the mainstay of AML management. Not only has this enhanced our understanding of the pathogenesis of AML,

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but also it has enabled us to categorize patients according to their molecular subgroups, to stratify their risk of relapse, and to develop targeted therapy against leukemia cells. So much so, that the molecular characteristics of each patient has helped us track the disease at its lowest technically possible level, namely the minimal or measurable residual disease (MRD) and to better describe complete remission and relapse status [5, 6, 8].

With the need for improved outcomes in AML patients who relapse post-transplant on the one hand, and the molecular advancement on the other, the search for a more durable remission and better survival rates ensues. Interventions can be made either in the maintenance setting where there is not yet evidence of relapse, in the pre-emptive setting in case of detectable MRD to avoid hematologic relapse, or in the therapeutic setting where there is overt disease relapse. In addition to targeted therapies that can be used based on the specific genetic aberrations tested, new approaches, such as biomodulatory drugs, a second allo-HSCT, and donor lymphocyte infusion (DLI) are all available therapeutic options post-transplant [9, 10]. In this review, we aim at providing an overview of prevention and treatment of relapse in AML patients who underwent allo-HSCT, including cell-based and pharmacologic options.

## Cell-based Therapy: Donor Lymphocyte Infusion (DLI)

### Therapeutic DLI

Relapse of AML after allo-HSCT can be related to the escape of tumor cells from the effect of pre-transplant conditioning chemotherapy and/or escape from post-transplant immune control [2]. In turn, these two mechanisms limit the expected immune response against malignant cells, thus contributing to relapse post-allo-HSCT. While the main aim was historically to reduce donor *T* cells in an attempt at lowering the probability of graft-versus-host disease (GVHD), studies have proven that *T*-cell depletion can, in fact, predispose to graft failure [11]. Despite full human leukocyte antigen (HLA)-matched HSCT, donor *T* cells can recognize antigenic structures on the surface of leukemic cells that are not included in the patient's HLA complex. The polymorphism in antigen peptides that triggers immune response even in patients who receive stem cells from HLA-matched donors is referred to as minor histocompatibility antigens [12, 13]. The escape of malignant cells from immune control, on one hand, and the potential role of donor *T* cells in producing allo-reactivity against minor histocompatibility antigens, on the other, introduces the use of donor *T* lymphocytes to develop adoptive immunotherapy as an effective cell-based therapy in the relapse setting.

A retrospective study conducted by the European Society for Blood and Marrow Transplant (EBMT)-Acute Leukemia Working Party (ALWP) included 399 patients with AML who had a first hematologic relapse after allo-HSCT and of whom 171 patients received DLI. Two-year OS was  $21 \pm 3\%$  for patients who received DLI compared to  $9 \pm 2\%$  for those who did not receive DLI. After controlling for confounding variables, the use of DLI remained an independent predictive factor of better OS ( $p=0.04$ ), in addition to young age ( $p=0.008$ ), and late relapse beyond 5 months after allo-HSCT ( $p<0.0001$ ). Moreover, the use of DLI seemed more beneficial and was associated with better OS in lower disease burden (less than 35% blasts in the bone marrow) ( $p=0.006$ ), disease remission ( $p<0.0001$ ), and in favorable cytogenetics disease ( $p=0.004$ ) [14]. Another study also conducted by the EBMT-ALWP included 263 AML patients who relapsed after RIC allo-HSCT. Among the 38 patients who achieved complete remission, consolidative DLI and/or allo-HSCT was associated with improved OS when compared to patients who did not receive cell-based therapy ( $55 \pm 11\%$  compared to  $20 \pm 10\%$ ). The survival benefit was not observed, however, among the 89 patients who did not respond to first-line chemotherapy and received DLI [15]. Despite the modest improvement in OS, the clinical benefit of DLI appears to be in low burden disease, or those who achieve remission before the infusion. Strategies to re-induce remission using chemotherapy, and recently, hypomethylating agents (HMAs)  $\pm$  targeted agents are important to implement before the use of therapeutic DLI.

In a study conducted across 46 sites in Japan, 100 patients who had relapse after allo-HSCT were included of whom 21 had AML. Eight of these 21 (38%) patients achieved complete remission following treatment with DLI with a probability of remaining in complete remission at three years of 7% [16]. Another Japanese study evaluating the main factors that can affect OS of AML patients after therapeutic DLI included 143 patients in first relapse following allo-HSCT. The strongest predictive factor for OS after DLI was complete remission status at the time of DLI, which was achieved in 8% of patients. Another factor that predicted better OS was a time interval between transplant and relapse of  $\geq 5$  months. When comparing these 2 predictive factors among patients in a subgroup analysis, the 2-year OS was 100% in patients who had complete remission and only 12% in those who had relapsed at  $\geq 5$  months post-transplant. This indicated again that DLI efficacy is mostly seen in patients who achieve complete remission, a factor limited to a minority of patients [17].

A study conducted by the Center for International Blood and Marrow Transplant Research (CIBMTR) included 1788 patients with AML with relapse after allo-HSCT between 1990 and 2010. Overall, 267 (15%) patients received DLI of whom 81% received it combined with chemotherapy. Of all

patients who received DLI, 24% underwent a second allo-HSCT. According to this study, two factors had a positive effect on survival, namely the use of a RIC/non-myeloablative regimen and a longer time from transplant to relapse. On the other hand, age greater than 41 years, unfavorable karyotype, mismatched unrelated donor, and GVHD at time of relapse were negative prognostic survivors. This study showed that a second transplant following the use of chemotherapy and DLI were associated with the best OS [18]. Second transplantation will be discussed further at a later stage in this review. Since cell-based therapy with DLI has greater efficacy in patients with lower tumor burden, those who achieve complete remission, and those who relapse beyond 5 months post-transplant, the study of prophylactic use of DLI to prevent relapse is ongoing.

### Prophylactic or pre-emptive DLI

The administration of DLI can induce a significant graft-versus-leukemia (GVL) effect. The use of DLI in the prophylactic setting stems back to 1995. Naparstek et al. used anti-CD52 for *T*-cell depletion in 146 allo-HSCT patients of whom 81 had AML. To induce the GVL effect, patients were transfused with increments of the donor's peripheral blood lymphocytes. Interestingly, administration of DLI was associated with GVHD and a significantly decreased relapse rate [19]. De Lima et al. investigated the use of DLI at 30, 60, and 90 days post-transplant after an RIC regimen with fludarabine 30 mg/m<sup>2</sup> for 4 days, melphalan 70 mg/m<sup>2</sup> for 2 days, and GVHD prophylaxis with cyclosporine 2 mg/Kg daily, tapered as of day 60. The study included 12 patients who were heavily pre-treated and with less than 6 months life expectancy of whom 4 had AML. High response rates and full chimerism were observed yet with an increased rate of GVHD. The DLI of  $1 \times 10^7$  CD3+ cells/Kg at day 30 post-allo-HSCT resulted in GVHD in half of the patients [20].

In an attempt to achieve the GVL effect and, at the same time, minimize GVHD, Dey et al. conducted a trial for patients with advanced hematologic malignancies of whom the majority had chemotherapy-refractory disease and underwent non-myeloablative allo-HSCT. Forty-two patients, of whom 4 had AML, had cyclophosphamide and anti-thymocyte globulin-based conditioning, in addition to thymic irradiation in case they had not received previous mediastinal radiation therapy. DLI was given prophylactically to 16 patients who had mixed chimerism and no evidence of GVHD at a dose of  $1 \times 10^7$  CD3+ cells/Kg as of week 5 post-transplant, while no DLI was given to the remaining 26 patients who had GVHD or early relapse. Eleven (69%) of those who received DLI achieved complete remission with a 1-year progression-free survival rate of 50%. Twelve (75%) of the patients who received DLI

had *T*-cell chimerism  $\geq 40\%$  at the time of DLI. These either converted to full donor chimerism (10 patients) or showed an increase in, or stable donor chimerism (2 patients) at day 100 post-allo-HSCT. Prophylactic DLI promoted sustained remission in patients with chemo-refractory hematologic malignancies. Also, the authors concluded that the degree of *T*-cell chimerism at the time of DLI administration can predict the outcome of mixed chimerism [21].

In the pre-emptive setting, DLI administration is based on the detection of MRD or mixed chimerism, determined by either molecular or immunophenotypic analysis, as these are signs of impending relapse. In fact, DLI has been shown to prevent relapse in patients with MRD-positive disease. Dominietto et al. studied the predictive role of MRD for relapse and the protective role of DLI against relapse, in 80 allo-HSCT patients of whom 36 patients had AML. The rate of relapse was highest (63%) among MRD-positive patients who did not receive DLI and lowest (6%) among MRD-positive patients who did receive it. Those who were MRD negative had a relapse rate of 16% (22).

Schmid et al. took a step forward and used DLI as prophylaxis in 75 high-risk allo-HSCT patients after an RIC regimen of whom 50 patients had AML. DLI was administered at day 120 post-allo-HSCT or 30 days following discontinuation of immunosuppressive drugs for patients who were in complete remission and did not develop GVHD. Dose of DLI was gradually increased 5- to tenfold, and a total of 3 doses were given within intervals of 4 to 6 weeks provided that no GVHD occurred. Twelve patients were eligible for prophylactic DLI; 11 of them had continuous complete remission with a 3-year leukemia-free survival of 92% from the time of transplantation. These impressive results could be explained by a time bias as the relatively delayed administration of DLI in this study, namely at 120 days post-transplant, can be related to the sustained remission [23].

A single-center prospective study by Liga et al. investigated the efficacy of prophylactic DLI in patients receiving allo-HSCT after an alemtuzumab-containing conditioning regimen. The rationale behind the use of low-dose alemtuzumab was to minimize the risk of GVHD. Indeed, 15 patients of whom 8 had AML received prophylactic DLI with a median number of 3 doses, with the first dose given at a median of 162 days post-transplant. Six (75%) of these patients converted from mixed to complete donor chimerism, and none of the patients who received prophylactic DLI relapsed [24]. Although alemtuzumab given prior to transplant can reduce GVHD, it can also increase the risk of mixed donor *T*-cell chimerism. As such, Solomon et al. investigated whether the early use of DLI in patients with mixed *T*-cell chimerism would decrease the risk of relapse without increasing the risk of GVHD. Prophylactic DLI was given at day 60 post-allo-HSCT before stopping immunosuppressive drugs to all 25 patients

with < 50% donor T-cell chimerism. Prophylactic DLI, given before stopping immunosuppression, was associated with a lower incidence of GVHD and a decreased rate of relapse [25]. In another study, prophylactic DLI was given to 27 patients who underwent allo-HSCT. All patients in the prophylactic DLI group lost their MRD positivity and had a significant reduction in blast counts, and no relapse occurred in this patient group. Regardless of the detection method, be it MRD or increasing mixed chimerism, prompt transfusion of pre-emptive DLI was found to be effective in prevention of relapse and overcoming MRD [26].

### Complications of DLI

Despite the benefit of DLI in controlling the disease by augmenting the GVL effect, and inducing long-term remissions, the most common complication of DLI is GVHD that could be life-threatening [11, 27]. The incidence of acute and chronic GVHD has been reported as 32% and 38%, respectively. In addition, prophylactic DLI is associated with less incidence of GVHD than therapeutic DLI with rates of 56% and 80%, respectively. Moreover, the dose of DLI was associated with the risk of GVHD. Administration of T cells greater than  $1 \times 10^8$  cells/Kg is associated with a risk of up to 50%, while administration of less than  $1 \times 10^7$  cells/Kg is associated with a risk as low as 10% [11, 28]. Despite the relatively elevated risk of GVHD, the risk of mortality remains low. According to Frey et al., while the incidence of acute and chronic GVHD can range between 40 to 60% and 33 to 61%, respectively, the mortality rate remains as low as 6 to 11% [29].

GVHD most commonly involves the skin, liver, and gut with reported incidences of 82, 41, and 41%, respectively [28]. Grade IV GVHD occurred in approximately 15% of the cases. Features of DLI-associated GVHD are generally similar to GVHD associated with allo-HSCT. The standard of care remains corticosteroids with a 55% response rate and 36% of patients requiring additional agents. Importantly, one-third of patients who developed acute GVHD had disease relapse [28]. Chronic GVHD and non-white ethnicity were independent risk factors for the development of GVHD following DLI [30].

Evidence from several studies on the use of CD8-depleted bone marrow grafts to reduce the risk of post-transplant GVHD has suggested the use of CD8-depleted DLI in an attempt to reduce this risk post-DLI [29]. A prospective study by Soiffer et al. compared the use of prophylactic CD8-depleted DLI to conventional DLI. Interestingly, none of the patients in the CD8-depleted DLI group developed GVHD, while 67% of patients in

the conventional DLI group developed GVHD [31]. The mechanism of bone marrow aplasia in this setting is not clear, and it was reported to be more common in the chronic phase of hematologic relapse in chronic myeloid leukemia than in AML [11].

### Cell-based therapy: second hematopoietic stem cell transplant

A different form of cell-based therapy is a second allo-HSCT with a new conditioning regimen followed by immunosuppression [9]. To our knowledge, there are no randomized trials that compare a second allo-HSCT to other therapy options. Available data are mainly from observational studies. Prospective trials are needed to better describe the role of second allo-HSCT. This is important, because patients in available retrospective and descriptive studies were positively selected by including patients who had survived until the intervention and who were younger than the majority of patients who relapsed after the first transplant [9, 32]. In one retrospective study from the EBMT-ALWP comparing the use of second allo-HSCT versus therapeutic DLI in patients with relapsed AML post-allo-HSCT, the OS was similar between the two groups. A total of 418 AML patients were included, of whom 137 underwent a second allo-HSCT and 281 received DLI for relapsed AML post-allo-HSCT. The reported 5-year OS was 19% and 15%, for the second allo-HSCT and DLI groups, respectively ( $p=0.86$ ) [33]. Another retrospective study included Japanese nationwide registry data for 1265 patients with AML suffering relapse after allo-HSCT. Relapse was observed after a median duration of 6.1 months, and the probability of OS after post-transplant relapse was 19% at 2 years with the interval from transplantation to relapse being the strongest indicator for OS. DLI and second allo-HSCT were given to 12% and 38% of patients, respectively. Interestingly, signs of survival benefit were seen when these procedures were done during complete remission (CR), while no benefit was seen when performed during non-CR. This study demonstrated the efficacy of a second transplant and emphasized the importance of developing effective bridging to cell-based therapies [34].

Multiple studies have reported various OS results of between 18 and 32% depending on study population, donor type, and conditioning regimen. A large retrospective study by Christopheit et al. included 179 patients of whom 132 had AML and 46 had acute lymphoblastic leukemia (ALL). The reported 2-year OS rate after the second allo-HSCT was 25%. On multivariate analysis, several factors were associated with better outcomes, namely more than 6 months between the first allo-HSCT and relapse and having had a matched related donor at the first allo-HSCT [32]. While the authors concluded that there was no advantage of donor change, it is generally recommended

to change the donor at second transplant. The rationale behind this is that with the first donor, the GVL effect was insufficient in controlling the leukemia [32]. As such, it would be reasonable to consider the use of a haplo-identical or unrelated donor for a second transplant, especially with the advancement in both techniques over the past decade [35]. In such cases, appropriate donor selection with a comprehensive HLA analysis for both the recipient and donor is recommended, since HLA loss may have contributed to relapse after the first allo-HSCT [9, 35].

Christopoulos et al. studied 58 patients with AML who relapsed after allo-HSCT and who were not suitable for DLI due to active GVHD or failed DLI. The 3-year OS rate was low at 18% with a high relapse rate of 56% [36]. Pawsan et al. analyzed 14 patients of whom 7 had AML, 5 had ALL, and 2 had refractory anemia with excess blasts, all of whom underwent a second allo-HSCT from the original donor. Overall survival was 60% at 58 months, and 13 of the 14 patients achieved complete remission [37]. A retrospective study by Orti et al. analyzed 116 patients with myeloid malignancies who underwent a second allo-HSCT after disease relapse (88 patients had AML). The 5-year OS was 32%. Factors that were associated with poor outcomes were time to second transplant of less than 430 days and having active disease on second transplant. An HLA-identical sibling donor for the second transplant was a good prognostic factor [38]. A retrospective analysis by Schneidawind et al. included 40 patients of whom 29 had AML and 11 had ALL. The 2-year OS rate was 32% [39].

The CIBMTR published a 3-year OS rate of 27% for 125 AML patients who received a second allo-HSCT [40]. The EBMT, on the other hand, reported a 5-year OS of 17% for patients with AML who underwent a second allo-HSCT [41]. Shaw et al. hypothesized that using a RIC regimen can decrease treatment-related mortality. A retrospective analysis of 71 patients who received a second allo-HSCT with an RIC regimen showed a predicted OS and treatment-related mortality of 28% and 27%, respectively. Their data support the hypothesis that RIC for second allo-HSCT is associated with less treatment-related mortality than myeloablative conditioning [42].

### Other cell-based therapy options

Discordance in minor histocompatibility antigens in matched donor transplants and in HLA in mismatched donor transplants can result in allo-reactivity in DLI or second transplants. As such, improving cell-based therapy options is an ongoing research goal. Selecting specific immune cells such as natural killer cells, or altering the cellular products, such as external cytokine stimulation or genetic alterations, are under investigation [9, 43].

Research into chimeric antigen receptor (CAR)-modified T cells for AML patients is underway. The challenge in this field is to identify AML target antigens. Examples of targets of current interest include CD123, CD33, FLT3, and CLL-1 [9, 44–46].

## Pharmacologic-based Therapy

### Isocitrate dehydrogenase (IDH) inhibitors

With the advent of molecular testing and widespread use of NGS, a large proportion of AML patients is evaluated for presence of targetable mutations that can be of clinical significance at diagnosis and relapse. Around 10–30% of AML patients have mutations in the gene encoding isocitrate dehydrogenase 1 (IDH1) or mitochondrial IDH2 [47–52]. The two mutations are usually mutually exclusive. These enzymes catalyze the transformation from isocitrate to ketoglutarate. Mutations in these enzymes lead to altered activity with production of 2-hydroxyglutarate. As a result, 2-hydroxyglutarate contributes to the impairment of cellular differentiation in the hematopoietic stem cells, thus inducing leukemogenesis [47–50]. Selectively targeting these mutations with IDH inhibitors has shown promising results in the setting of relapsed/refractory (R/R) AML with reported complete remission rates of around 30% for ivosidenib and enasidenib [48, 53]. Accordingly, the Food and Drug Administration (FDA) has approved both drugs in the setting of R/R AML [9]. A study by DiNardo et al. investigated the role of ivosidenib, a selective IDH1 inhibitor, in patients with R/R *IDH1*-mutant AML. The median OS was 8.8 months with half of the patients achieving complete response after 18 months of follow-up [48]. Another study investigated combining ivosidenib with azacitidine and was stopped when the combination showed excellent results (AGILE, NCT03173248). Enasidenib, a selective IDH2 inhibitor, was also studied in patients with R/R *IDH2*-mutant AML. In a phase I/II study, 20% of patients achieved complete remission and an objective response rate of 40.3% [53]. Response was significantly associated with less comutation burden [48, 53]. Trials for IDH-mutant AML patients included a limited number of patients with relapse after transplant. There are only a few ongoing trials on the use of IDH inhibitors for *IDH*-mutant AML patients who have relapsed following allo-HSCT. The effectiveness of this drug, being an orally administered and with a good safety profile, makes it an ideal agent for maintenance post-transplant. As such, it is currently being tested in this setting. An ongoing phase I trial is evaluating the efficacy of enasidenib for *IDH2*-mutant AML following allo-HSCT (NCT03515512), and another trial is evaluating the role of enasidenib as maintenance therapy in

this patient population (NCT03728335). The efficacy of ivosidenib for *IDH1*-mutant AML following allo-HSCT is also being evaluated (NCT03564821).

### Hypomethylating agents

Hypomethylating agents (HMAs), such as decitabine and azacitidine, show efficacy when used in induction for AML patients, especially in older patients who may not tolerate more intensive chemotherapy [54, 55]. Azacitidine can enhance the GVL effect after transplant, thus promoting better disease control, by increasing the expression of human leukemic antigen DR-1 among other tumor associated antigens. In addition to anti-leukemic activity through DNA hypomethylation, HMAs have immunomodulatory activity that enhance the activity of regulatory *T* cells and cytotoxic *T* cells, both of which play an important role in regulating GVHD while maintaining the beneficial GVL effect [56–59].

One retrospective study investigated the use of low-dose azacitidine in nine patients who had disease recurrence after allo-HSCT, and a 37.5% relapse rate was observed. Five remained alive with complete remission on follow-up [60]. A phase I dose-finding study by De Lima et al. used different escalating doses of azacitidine maintenance in 37 heavily pre-treated AML patients post-allo-HSCT, in addition to eight patients with myelodysplastic syndrome (MDS). The use of low-dose azacitidine at 32 mg/m<sup>2</sup> for 5 days was found to be the optimal dosing. One-year OS was 77% and the relapse rate was 53% [61]. In addition to its efficacy, azacitidine can increase the number of immunomodulatory *T* regulatory cells within the first 3 months of transplant, which supports the use of azacitidine after transplant as a mechanism of augmenting the GVL effect without increasing GVHD risk [58]. Interestingly, the use of azacitidine in the post-allo-HSCT setting reduced the risk of relapse particularly in patients who had a CD8+ T-cell response to tumor antigens as shown in the RICAZA trial [62]. Platzbecker et al. studied azacitidine as pre-emptive treatment after MRD detection determined by donor chimerism analysis of CD34+ blood cells in patients with MDS or AML after allo-HSCT [63]. After this trial, Platzbecker et al. proceeded with the RELAZA2 prospective study, showing that prophylactic use of azacitidine can delay relapse in patients with high-risk AML who achieve complete remission after allo-HSCT. The study included 172 patients with AML and 26 patients with MDS who had achieved complete remission after conventional chemotherapy or allo-HSCT. At 1 year, relapse-free survival was 46% in the 53 patients who were MRD-positive and who received azacitidine. This reinforced the role of pre-emptive azacitidine in preventing and/or delaying relapse in MRD-positive patients with AML or MDS [64].

In addition, an observational study by El-Cheikh et al. demonstrated that the use of low-dose azacitidine in a post-transplant preventive or maintenance setting until disease progression can reduce the risk of relapse and induce a durable remission in patients with high-risk AML or MDS [65].

A confirmatory phase II randomized trial by Oran et al. evaluated the efficacy of maintenance azacitidine in the post-transplant setting. This trial had difficulty in recruiting patients and included 187 AML patients post-allo-HSCT. The median number of azacitidine cycles received was only 4 cycles. While there was no significant difference in relapse-free survival and OS, the results showed that a prospective trial in this setting is feasible yet challenging [66]. Another multicenter randomized trial was conducted in China and included 204 high-risk patients with AML who underwent allo-HSCT and achieved MRD negativity. Minimal-dose decitabine combined with recombinant human granulocyte colony-stimulating factor after allo-HSCT resulted in a reduction in the relapse rate with a 2-year relapse rate of 15% compared to 38% ( $p < 0.01$ ) in patients who did not receive maintenance treatment [67]. On the other hand, a few studies have suggested that AML may not benefit from HMAs after allo-HSCT. A retrospective study by Maples et al., for example, included 25 patients of whom 18 had AML. There was no difference in time to hematologic relapse and OS, and maintenance therapy was stopped early in 72% of patients due to GVHD, relapse, or intolerance [68].

In a prospective study by De Lima et al., an oral form of azacitidine, CC-486, was well tolerated with a one-year relapse rate of 21% in transplant patients with AML or MDS [69]. A randomized phase 3 trial to confirm its efficacy and safety is in development.

### Venetoclax

A selective inhibitor of *B*-cell lymphoma-2 (BCL-2), venetoclax, has shown effective results in combination with HMAs or low-dose cytarabine in patients with newly diagnosed AML, especially those who are unfit for intensive chemotherapy [70, 71]. DiNardo et al. showed that the combination of venetoclax with decitabine or azacitidine was well tolerated and effective in treatment-naïve elderly patients with AML, with 67% of patients achieving composite complete remission [72]. In another study by Wei et al., a combination of venetoclax with low-dose cytarabine in treatment-naïve AML patients who were ineligible for intensive treatment showed an improved complete remission rate from 8 to 26% [71]. As a result of these trials, the combination of venetoclax with azacitidine or low-dose cytarabine is FDA approved for patients who are treatment-naïve and unfit for induction chemotherapy due to older age (> 75 years) and/or comorbidities [7].

**Table 1** Take-home messages

Cell-based therapy	
Donor lymphocyte infusion	<ul style="list-style-type: none"> <li>√Most effective in certain conditions, including low tumor burden and loss of chimerism or MRD</li> <li>√Favorable prognostic factors:               <ul style="list-style-type: none"> <li>●Use of an RIC/non-myeloablative conditioning regimen</li> <li>●Longer time from transplant to relapse</li> </ul> </li> <li>√Poor prognostic factors:               <ul style="list-style-type: none"> <li>●Age greater than 41 years</li> <li>●Unfavorable karyotype</li> <li>●Mismatched unrelated donor</li> <li>●GVHD at time of relapse</li> </ul> </li> </ul>
Second hematopoietic stem cell transplant	<ul style="list-style-type: none"> <li>√Prospective trials needed to better describe their role</li> <li>√Available data including patients who have survived until the intervention and who were younger than the majority of patients who relapse after the first</li> <li>√Favorable prognostic factors:               <ul style="list-style-type: none"> <li>●More than 6 months between the first transplant and relapse</li> <li>●Matched related donor at the first transplant</li> </ul> </li> </ul>
Others	<ul style="list-style-type: none"> <li>√CAR-T cells underway for AML patients</li> <li>√Challenge to identify AML target antigens: CD123, CD33, FLT3, and CLL-1</li> </ul>
Pharmacologic-based therapy	
Isocitrate dehydrogenase (IDH) inhibitors	<ul style="list-style-type: none"> <li>√Promising results in the setting of relapsed/refractory AML</li> <li>√Ongoing trials for IDH-mutant AML patients who relapsed following allo-HSCT</li> </ul>
Hypomethylating agents	<ul style="list-style-type: none"> <li>√Anti-leukemic activity through DNA hypomethylation</li> <li>√Immune modulatory activity that enhances the activity of regulatory T cells and cytotoxic T cells</li> <li>√Regulating GVHD while maintaining the beneficial GVL effect</li> <li>√The optimal dose used is 32 mg/m<sup>2</sup> for 5 days every 28 days</li> </ul>
Venetoclax	<ul style="list-style-type: none"> <li>√Role in targeting leukemia cells with an acceptable toxicity profile</li> <li>√Venetoclax combination therapy: similar anti-leukemia effect yet a better toxicity profile than FLAG-idarubicin</li> <li>√Reduction and/or interruption of dosing may be warranted in some cases of neutropenia</li> </ul>

Given the role of venetoclax in targeting leukemia cells and its favorable toxicity profile, its role as post-transplant maintenance for AML patients who have a high risk of relapse was studied by Kent et al. [7]. Venetoclax as a single agent was well tolerated as maintenance post-transplant for high-risk AML patients who underwent transplant with a relapse-free survival rate of 87%. However, 4.8% of patients had holding of venetoclax or dose reduction due to myelosuppression. The optimal dose and duration of venetoclax needs further elucidation [7]. Two ongoing clinical trials, NCT04161885 and NCT04128501, are evaluating the role of venetoclax combined with azacitidine as maintenance therapy post-transplant. Data on venetoclax post-transplant as salvage therapy remain limited.

A retrospective study by Zucenka et al. compared the outcome of 20 patients who received venetoclax, low-dose cytarabine, and actinomycin D to 29 patients who received FLAG-idarubicin as salvage therapy for AML relapse post-transplant. The overall response rate was 75% in the venetoclax group, compared to 66% in the FLAG-idarubicin group, yet the difference was not statistically significant ( $p=0.542$ ). Treatment-related mortality, however, was 0% in the venetoclax group, compared to 34% in the FLAG-idarubicin group. The authors concluded that venetoclax combination therapy

had a similar anti-leukemia effect but a better toxicity profile than FLAG-idarubicin [74, 75].

Being myelosuppressive, especially when combined with other agents, venetoclax can result in prolonged pancytopenia. While data on guidance for use of venetoclax after transplant are limited, experience from a few institutions has helped provide general consensus in that regard. Since it is a low-intensity regimen, patients will generally need more than a cycle to reach an adequate response. If the bone marrow evaluation shows hypoplasia and no evidence of AML, monotherapy with venetoclax while withholding the other agent, such as an HMA or low-dose cytarabine, can allow count recovery. Even with this approach, it is worth noting that venetoclax dose reduction may still be warranted in some cases of neutropenia. Studies are needed to evaluate whether interruption of dosing can be an effective regimen with a better toxicity profile than continuous dosing [74, 76].

## Conclusions

Table 1 summarizes the take-home messages from this review paper. FLT3 inhibitors, which are the topic of another section tackled in this review series, have demonstrated a significant improved relapse-free survival and OS

in *FLT3*-ITD mutant AML (52, 77, 78). The risk of AML relapse post-allo-HSCT remains a challenge. Significant progress has been made to reduce non-relapse mortality and to enhance durability of remission. When applying data from available studies on R/R AML, clinicians should use it with caution, especially with regard to the treatment received in the frontline setting and the residual toxicity. Outcomes for AML relapse remain limited due to the toxicities of the salvage treatment. Post-transplant maintenance therapy is usually deployed in patients who are MRD negative in complete remission, while pre-emptive treatment refers to therapy administered upon detection of MRD. Both scenarios aim at providing prophylaxis against disease relapse. Prophylactic therapeutic options require the use of safe therapies that will minimize additional toxicity to the patient. In case of relapse, defining the molecular profile is essential; NGS should be considered for relapsed bone marrow specimens prior to initiation of salvage therapy. Patients who have persistent targetable mutations can benefit from targeted therapy. Although there are several limitations in clinical practice for DLI, it remains a powerful example of adoptive immunotherapy and an established salvage and prophylactic option post-transplant. DLI is most effective in certain conditions, including low tumor burden and loss of chimerism or MRD. As such, DLI use in the prophylactic setting, before a relapse becomes evident, should be considered. The risk of relapse post-transplant should be taken into consideration. Another important consideration is the time between allo-HSCT and DLI administration, where shorter intervals can represent a greater risk for developing GVHD. Other cell-based therapies, including CAR-T cells, have led to enhanced durability of remission in lymphoid neoplasms and research into their role in AML is underway.

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## Declarations

**Conflict of interest** All authors declare that they have no conflict of interest

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