Journal of
Cancer Research and Therapeutic Oncology

JScholar
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Research Article Open Access

Novel Therapies and Strategies for Relapsed Acute Myeloid Leukemia Post-Allogeneic Stem Cell Transplantation

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Received Date: July 03, 2024 **Accepted Date:** July 03, 2024 **Published Date:** July 06, 2024

Citation: Max Duesberg, Gary Schiller (2024) Novel Therapies and Strategies for Relapsed Acute Myeloid Leukemia Post-Allogeneic Stem Cell Transplantation. J Cancer Res Therap Oncol 12: 1-12

Abstract

Acute myeloid leukemia (AML) is a challenging hematologic malignancy often requiring allogeneic hematopoietic stem cell transplantation (allo-SCT) for high-risk patients. Despite allo-SCT being a potentially curative treatment due to the graft-versus-leukemia (GVL) effect, relapse occurs in up to 50% of patients, leading to poor prognosis with median overall survival from relapse being less than five months. Factors influencing poor outcomes include short remission duration post-transplant, advanced disease, older age, unrelated donor use, and prior graft-versus-host disease (GVHD). Immunologic mechanisms such as downregulation of HLA Class II and immune checkpoint upregulation allow leukemic cells to evade the GVL effect. Current salvage therapies, including donor lymphocyte infusions (DLI), hypomethylating agents, and targeted therapies, offer limited success, highlighting an urgent need for novel treatment strategies. This review discusses current treatment approaches for AML relapse post-allo-SCT and explores potential strategies for clinical trial designs to prevent or address relapse in high-risk leukemia patients.

Keywords: Acute Myeloid Leukemia (AML); Hematopoietic Stem Cell Transplantation; Graft-Versus-Leukemia; Acute Myeloid Leukemia; Stem Cell Transplantation

Introduction

For over 60 years, allogeneic hematopoietic stem cell transplantation (allo-SCT) has remained an important and potentially curative treatment strategy for patients with intermediate- to high-risk acute myeloid leukemia (AML). Owing to cytoreductive conditioning and the immune-mediated graft-vs- leukemia effect, allo-SCT represents one of the most potent cellular immune therapies for hematologic malignancies used in clinical practice (1). Allo-SCT leads to improved overall survival and leukemia free survival with intermediate or poor risk cytogenetic routes (which compromises 90% of newly diagnosed AML patients) compared to non-transplant approaches (47). Recent advances in transplant technology have further helped to increase donor availability and reduce transplant-related toxicity [1]. Allo-SCT provides patients the greatest likelihood of long-term survival for those with disease at greatest risk of relapse [42]. Unfortunately, up to 50% of patients sustain eventual relapse even after allo-SCT in this disease setting [2]. Salvage therapies are rarely successful, and the prognosis for those patients who relapse following transplantation remains dismal, with two-year survival of less than 20% and a median overall survival from relapse, in one study, of 4.7 months [3]. Factors influencing low likelihood of survival after allogeneic transplant include brief duration of remission after a prior transplant, advanced disease based on biologic risk factors, older age, use of unrelated donor, and acute graft-versus-host disease before relapse [3]. Based on retrospective analyses, the Center for International Bone Marrow Transplant Registry (CIBMTR) reported a 3-year overall survival (OS) rate of only 4% among AML patients who relapsed within 6 months of allogeneic hematopoietic cell transplantation [48]. Regrettably, early relapses are common, with a median time to post-transplant relapse of 7 months, and 43% of relapses occurring within 6 months [48]. On the other hand, a major factor that predicts for survival for patients after relapse is prolonged remission after first transplant. The Center for International Bone Marrow Transplant Registry showed that lower mortality was associated with longer time from allo-SCT to relapse with a relative risk of 0.55 for 6 months to 2 years, relative risk of 0.39 for 2-3 years, and a relative risk of 0.28 for greater than 3 years [4]. There is strong evidence supporting the GVL effect in AML, which is mediated by T lymphocytes and is associated with the development of GVHD. Both acute and chronic GVHD after transplant have been shown to reduce the risk of post-transplant relapse [49,50]. This indicates that post--transplant alloimmune effects can both prevent relapse (GVL) and cause side effects (GVHD). Notably, patients who relapse despite developing GVHD have poorer survival [48], likely due to the combined morbidity of GVHD and the ineffectiveness of the GVL effect in these patients. It has also been shown that there are certain immunologic mechanisms that have a role in relapse after allo-SCT such as the dysregulation of immune pathways and downregulation of MHC class II genes [5]. Nearly 50% of patients who relapse after a transplant exhibit downregulation of HLA Class II on leukemic blasts, regardless of the number of donor-recipient HLA incompatibilities. This is not observed in AML patients who relapse following chemotherapy alone (50, 51). In AML patients who underwent HLA haploidentical transplant, up to one-third of relapsed patients experience HLA haplotype loss due to acquired uniparental disomy of chromosome 6p, rendering donor lymphocytes unresponsive to these relapsed leukemic blasts in vitro [53,54]. Consequently, the downregulation of HLA Class II molecules or the loss of the non-shared HLA haplotype allows leukemic blasts to evade the GVL effect. Upregulation of inhibitory checkpoint molecules could allow leukemia progenitor cells to evade donor-derived T cells [5]. Additionally, it has been demonstrated that there may be dysregulation of multiple costimulatory ligands on AML blasts with changes in donor T cells at post-transplantation relapse (6). Memory T cells may have increased expression of inhibitory receptors in patients who sustain relapse compared to those who do not, leading to so-called T cell exhaustion [6]. Such T cells demonstrate dysfunctional effector functions, restricted TCR repertoire, and decreased leukemia-reactive specificities.

Considering the high rate of recurrence, and poor prognosis in the setting of allotransplant for high-risk leukemia, there is an urgent unmet need to develop novel therapies for this patient population that decrease risk of post-transplant relapse. At present, several investigational options exist for these patients, including maintenance therapy after transplant with hypomethylating agents, or targeted small-molecule inhibitors; post-transplant prophylactic donor-lymphocyte infusions; or post-relapse interventions

such as second allogeneic stem cell transplantation. Unfortunately, there remains no established standard-of-care therapy for AML patients who relapse after transplantation.

In this review we provide an overview of current treatment approaches available for patients with acute myeloid leukemia who relapse after allo-HSCT and discuss potential strategies for the design and implementation of new clinical trials that either address the problem of relapse, or prevent relapse in the setting of high-risk leukemia.

Donor Lymphocyte Infusion

Donor Lymphocyte Infusion (DLI) has been shown to induce remission in post-allo-HCT patients with CML who relapse [7]. The infusion of donor lymphocytes has shown to induce complete remission in many patients post-allo-HCT [43]. A patient's response is generally driven by the stage of their treatments as well as a shorter time interval between transplant and DLI infusion [43]. Encouragingly, the durability of treatments in CML is strong, with some patients maintaining cytogenetic remission up to or beyond 70 months after DLI [43]. Patients with only molecular and cytogenetic relapses almost always achieved remission with DLI, whereas those with chronic phase hematologic relapse went into remission approximately 75% of the time. Patients in the accelerated or blastic phase were less responsive to DLI, with response rates ranging from 12.5% to 33% [55]. On the other hand, in AML, the effect is not as strong. This could be partially attributed to the characterized immunoediting capabilities of post-transplant AML with downregulation of HLA Class II genes or loss of haplotype [56]. This raises the possibility that DLI could be ineffective in relapses involving this underlying mechanism of immune evasion [56]. Still, In a retrospective analysis done on 399 patients with AML in their first hematological relapse after allogeneic hematopoietic stem cell transplantation (HSCT), patients receiving DLI, compared to those who did not, had an estimated survival at 2 years was 21% +/- 3% and 9% +/- 2%, respectively [7]. In the group of patients receiving DLI, favorable cytogenetics, a tumor burden of less than 35% bone marrow blasts, female sex, as well as favorable molecular features all increased survival in a multivariate analysis. Furthermore, patients who relapsed more than 5 months after HSCT and were younger than 37 years had better outcomes [7]. Of the 171 patients that received DLI, 35% achieved remission [7]. However, 43% developed acute graft-versus-host disease (GVHD) while 46% developed chronic GVHD [7]. One measure taken for patients after haploidentical stem cell transplant is post-transplant cyclophosphamide for the prevention of post-transplant GVHD [44]. DLI may be more effective in these patients. When it has been used in these patients who have experienced relapse small incremental doses of haploidentical CD3-positive cells are administered due to the very likely probability of inducing severe acute GvHD [44]. One retrospective analysis analyzed pediatric patients with myeloid malignancies who had gotten prophylactic DLI as well as post-transplant cyclophosphamide [46]. The incidence of grade 2-4 GVHD was 37% while the incidence of grade 3-4 GVHD was 16.7% [46]. The 2 year rate of moderate to severe chronic GVHD was 8.1% (46), demonstrating that in this pediatric population, prophylactic DLI with post-transplant cyclophosphamide does still carry a substantial risk of GVHD, but appears to be relatively effective and safe and justifies further research in adult populations. While remission may be achieved, and survival may be increased in patients receiving DLI under the circumstances of prior haploidentical transplant, understanding the consequences of DLI is important when deciding which patients are candidates.

There is new research demonstrating that DLI in combination with certain chemotherapeutic agents can elicit greater likelihood of responses [8]. Low-dose azacitidine has been shown to upregulate silenced tumor antigens that can induce a cytotoxic T-cell response. In a multi-center retrospective analysis consisting of 154 relapsed AML/MDS (AML, n = 124; MDS, n = 28; MPN, n = 2) patients receiving hypomethylating agent/DLI combination, the overall response rate was 33%, and the CR rate was 27% [7]. Conveniently, no patient experienced grade 3-4 GVHD from the combined treatment. Another hypomethylating agent that has been studied in conjunction with DLI is decitabine, that also showed efficacy in combination with DLI. A retrospective multicenter analysis from Germany reported that decitabine plus DLI achieved an ORR of 25% and CR of 17% in 36 patients with relapsed AML (n = 29) [8].

Hypomethylating Agents

Two hypomethylating agents (HMA) commonly used in post-transplant relapsed AML patients are azacitidine and decitabine. They serve as the backbone for many combination therapies due to the ability to induce immunologic activity against tumors while having reduced toxicities [9]. In one study, azacitidine alone was shown to induce complete remission in 6 out of 10 patients treated with myeloid malignancies after allo HCT, and the median overall survival for the group was 422.5 days. However, 3 patients had leukemia progression after a median of 6 cycles and 1 died as a result [12]. Notably, there were no flares of GVHD observed in these patients [12].

Azacitidine is a potent demythylating agent that can induce upregulation of cancer-testis antigens. As a result, this upregulation can present as an easier target for allogeneic T-cells. Additionally, this agent is known to spur the expression of HLA class 1 antigens and costimulatory molecules on tumor cells, allowing allogeneic T cells to distinguish leukemia cells [10,13]. HMAs can induce the expression of FOXP3 in CD4(+)CD25(-) T cells [11], that cause these cells to convert from non T regulatory cells into T regulatory cells with T suppressor function, which decreases the likelihood of GVHD in these patients [11,14].

There have been mixed results from studies using HMAs as prophylaxis. In a retrospective review, 25 patients received azacitidine prophylactically following myeloablative allogeneic HCT and were matched to historical controls and there was no difference in hematologic relapse, overall survival, or non-relapse mortality [15]. However, another study observed patients receiving oral azacitidine post allo HCST. These patients had a low overall rate of relapse of 21% in the first year and had low rates of treatment related complications [38]. The use of maintenance therapy remains a controversial and unclear option for patients post allo HCST; however, there could be potential prophylactic use for patients given its tolerability.

Targeted Therapy

AML tends to be associated with fewer mutations than other cancers, averaging around 13 mutations per cell [16]. The most common gene mutations and their estimates of frequency in *de novo* AML include NPM1 (27%), FLT3 (28%), DNMT3A (26%), and IDH1/IDH2 (20%) [16]. These mutations present unique therapeutic targets and several agents have been tested in AML patients as therapy, and as maintenance to prevent relapse after allotransplant.

For AMLs with IDH1 mutations, ivosidenib has been an effective agent. IDH1 mutations are observed in approximately 7% of AML patients [16]. In one study examining the efficacy of ivosidenib as a monotherapy in relapsed AML characterized by the mutation, partial hematologic recovery was achieved in 30.4% of patients, complete remission in 21.6% of patients, and the overall response rate was 41.6% [17]. Among patients with AML in complete remission with partial hematologic recovery and complete remission with complete hematologic recovery, 21% had no detectable IDH1 mutations on digital polymerase chain reaction assay [17]. Unfortunately, the registration study was not done in the post-transplant setting, but given promise results, ivosidenib warrants further investigation. Olutasedanib is another agent that targets IDH1 mutations [44]. In a recent Phase 1/2 multi-center study, patients with confirmed AML or high risk MDS received olutasidenib or olutasidenib plus azacytidine [44]. Patient were then further divided by prior treatment and one cohort of patients was a subset who had undergone prior allo HSCT [44]. Of the 31 patients in this group, 19% had CR, 10% had CR with incomplete count recovering. For the 10% of patients with responses, the median duration of their response was around 7.1 months [44]. While these are early study and longer-term studies are needed studying olutasidenib, the results are promising in a post allo HSCT setting.

Enasidenib targets IDH2 mutations in AML [18]. One trial demonstrated that 19.6% of patients with relapsed/ refractory IDH2-mutated AML attained complete remission when teated with enasidenib [18]. The median overall survival for all patients was 8.8 months [18]. Enasidenib was well tolerated throughout the trial and induced molecular remissions with minimal adverse effects for many patients whose disease had failed to respond to other AML treatment regimens such as re-induction chemotherapy and other lower-intensity regimens [18]. Additionally, for patients with relapse post allo HCT, overall response rate to Enasidenib was 35%, demonstrating that it can potentially

be used as an agent by itself post-relapse and allo HCT [18]. Enasidenib has been also used as a maintenance therapy in patients post-allo HCT. One multicenter phase 1 trial of maintenance Enasidenib showed a cumulative incidence of relapse of 16% and a two-year progression-free and overall survival of 69% and 74% respectively [39]. It was well tolerated and safe for patients during the trial as well, suggesting Enasidenib could also be explored as a maintenance therapy.

Another therapeutic target is FLT3, which is commonly mutated in AML. Sorafenib is a multi-target kinase inhibitor of FLT3 [40]. One retrospective cohort examined 29 relapsed patients with FLT3-ITD-positive AML post-allo BMT who received sorafenib as monotherapy, 21% achieved sustained CR, with four of these patients having treatment-free remission for a median of 4.4 years [40]. This study demonstrates that sorafenib may be an option for very poor risk FLT3 ITD-mutated AML patients who have relapsed after allo-BMT.

Gilteritinib is a selective FLT3 inhibitor with activity against relapsed and refractory FLT3-mutated AML [20]. In one phase 3 randomized trial, patients with relapsed or refractory FLT3-mutated AML either received gilteritinib or salvage chemotherapy [20]. The median overall survival in the gilteritnib group was 9.3 months compared to 5.6 months in the chemotherapy group [20]. The median event-free survival was 2.8 months in the gilteritinib compared to 0.7 months in the chemotherapy group [20]. Additionally, in patients who had previously undergone allo-HCT, gilteritinib-treated patients had an improved response rate of 36% compared to 18% for non-transplant patients (20), suggesting a basis for treatment with gilteritnib in patients who are FLT3 positive with AML post-transplant possibly attributable to renewed donor chimerism [20].

Another new agent, quizartinib, which is also a mutant FLT3 inhibitor has been shown to have antitumor activity in patients with FLT3-positive AML [21]. One study compared the effects of quizartinib versus placebo on overall survival in patients with newly-diagnosed FLT3-positive AML who were treated with 7+3 induction chemotherapy and demonstrated that the median overall surivival in the quizartinib group was 31.9 months compared to the placebo group which was 15.1 months [21]. The use of Quizartinib as a single agent to reinduce remission in the post-allotransplant relapsed setting remains to be demonstrated.

Crenolanib is also a tyrosine kinase inhibitor with activity against mutated FLT3 [22]. In one study, patients were started on induction chemotherapy, then consolidated with high-dose cytarabine and or allogeneic transplant, patients were then given crenolanib as maintenance [22]. The study demonstrated an 86% overall response rate with 77% of patients achieving complete remission [22]. Median event-free survival was 44.7 months with 55% of patients were alive after 3 years [22]. Whether this represents an improvement over what might have been achieved without crenolanib is not known, and will likely not be demonstrated since a phase 3 trial was terminated [22].

Immunotherapy

Immunotherapy beyond what can be achieved by allotransplant itself remains to be exploited in relapsed AML. Current evidence suggests that the graft-vs leukemia effect in the transplant setting is predominantly, but not exclusively, mediated by T lymphocytes and that T cell-mediated recognition of recipient clonal cells could lead to further routes of treatment [23].

An interesting concept often utilized in practice is early discontinuation of immunosuppression after allogeneic transplant. A prospective study examined hematopoietic chimerism post-allo-BMT [24]. The study demonstrated, as expected, that patients with increasing recipient chimerism over time carried a significantly enhanced risk of relapse ($P < 0.0001$; odds ratio 37) [24]. In contrast, patients with mixed hematopoietic chimerism after engraftment followed by later achievement of complete donor chimerism were more likely to remain in remission (24). These findings indicate that interventions such as immunosuppression associated with decreased donor chimerism may increase the likelihood of relapse. In a study investigating patients with AML and MDS who sustain relapse after transplant, the discontinuation of immunosupresseion eventually led to a low probability, 6.6%, of complete remission [25]. Whether earlier discontinuation of immunosuppression in patients post-allo-BMT would have been more effective is a subject for study. A randomized trial of early discontinuation of immu-

osuppression would have to analyzed the impact of withdrawal on graft versus host disease (GVHD).

One mechanism of relapse of AML post allo-BMT is by evasion of the donor immune system. Leukemia cells may engage cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) and programmed death 1 (PD-1) receptors through their own ligands such as B7-1, B7-2, PD-L1, and PD-L2 and, as a result, neutralize effector T-cell function and block antitumor activity [26]. The CTLA-4 directed agent ipilimumab has been proposed as an immunotherapy for patients post-allo-BMT [26]. A multicenter phase 1 trial investigated ipilimumab in patients with relapsed AML post-allo-BMT and found that 23% of patients had a complete response, 9% had a partial response, and 27% had decreased tumor burden [26]. Additionally, these responses likely caused the infiltration of T cells, expansion of effector T cells, and decreased the activation of regulatory T cells [26]. However, side effects such as GVHD and immune-mediated toxic effects were seen in 21% of patients [26]. PD-L1 is also a target of immunotherapy with the agent nivolumab. In a phase 1 multicenter trial for patients with relapsed leukemias after allo-HCT, the overall response rate was 32% with a 1-year progression-free-survival rate of 23% and an overall survival rate of 56% [27]. Unfortunately, similarly to ipilimumab, there was nivolumab-related immunologic toxicity in 18% of patients including 2 deaths from GVHD [27]. While adverse events are expected with the use of ipilimumab and nivolumab, immunotherapy checkpoint inhibitors also demonstrate another avenue of approach for patients in relapse post-allo-BMT, and stress the importance of finding strategies that might ameliorate toxicity while maximizing efficacy

CD33 is a common receptor protein expressed both on leukemic blasts and normal myeloid progenitor cells [28]. Gemtuzumab was the first approved antibody--drug conjugate by the FDA and specifically targets CD33 [28]. Although Gemtuzumab was associated with a toxicity signal of hepatic veno-occlusive disease [29], new data suggest less risk for gemtuzumab administered in a fractionated dosing schedule [30]. Additionally, in a phase 3 trial, 26% of patients with relapsed/refractory AML who received fractionated doses of gemtuzumab with chemotherapy achieved complete remission [31] with low risk of hepatotoxicity. One study specifically looked at patients with AML relapsing after allo HCT and were treated with gemtuzumab as well as intensive chemotherapy [41]. The overall response rate in this study was 72% as well 7 complete remissions with remarkably no evidence of patients enduring veno-occlusive disease and patients primarily only dealing with a transient transaminitis [41]. These findings combined with the new data suggesting gemtuzumab's safety profile suggest it as another option for patients who relapse after allo HCT.

Bifunctional monoclonal antibodies are a new therapy gaining traction (34). This therapy works by having two dual variable regions that bind to CD3 on cytotoxic T lymphocytes and tumor cell antigens [34]. This in turn activates the effector function of T lymphocytes and releases cytokines causing the destruction of the tumors they bind to [34]. Flotetuzumab is a bispecific antibody molecule to CD3 and CD123, which binds both to the tumor and effector T cells [34]. In a phase 1/2 study of relapsed/refractory AML patients, flotetuzumab induced complete remission in 26.7% with an overall response rate of 30%, leading to a median overall survival of 10.2 months [34]. The main side effects seen were infusion related reactions and cytokine release syndrome grade 1-2 [34]. Unfortunately, compared to B-cell immunotherapies, the common target antigen expression on macrophages and monocytes may lead to an increased frequency and severity of these infusion reactions [34]. However, strategies such as pretreatment with dexamethasone, use of tocilizumab, stepwise dosing during the first week of administration, and dose reductions and temporary interruptions of treatment were shown to decrease severe infusion related reactions [34]. Further investigations into the efficacy of Flotetuzumab are needed as well as potentially other bifuncitonal monoclonal antibodies for other targets, but the early results are encouraging and demonstrate another potential path for AML patients post-allo-BMT.

CAR T cells are an approved treatment for ALL and is now being considered for patients with AML. CAR T cell therapy has been shown to be effective in patients with CD38 positive AML post-allo-BMT [35]. One study showed that 4 of 6 patients achieved complete remission, and the median overall survival time was 7.9 months, while all pa-

tients had manageable side effects [35]. Another CAR T cell therapy examined was one targeting patients with CD33 positive AML [36]. A phase 1/1b trial studying patients with refractory or relapsed AML, with which 15/24 patients had previously undergone allo-BMT, were given CAR T cells targeting CD33 and had an encouraging response of 50% following lymphodepletion [36]. While safety and toxicities need to be further examined for patients receiving CAR T therapy, patients with ALL receiving CAR T therapy have similar 12-month overall survival rates regardless if the patients had received allo-HCT prior suggesting that prior allo-HCT likely would not increase the risk of mortal CAR T therapy toxicity for patients with AML [37]. There will also need to be more studies with larger patient populations to continue to examine CAR T's efficacy, but the approach shows promise and has been revolutionary in the field of ALL treatment and deserves further consideration for patients with AML.

Another promising therapy that has been used recently is Orca-T [45]. Orca-T is an immunotherapy that is made from allogeneic donors which is comprised of stem and immune cells which turn on donor regulatory T cells to control alloreactive immune responses [45]. One phase 2 study examined 32 patients with AML who had received Orca-T and 81% of these patients had relapse free survival at both 1 year and 18 months [45]. Additionally, greater than grade 3 GVHD rates were low at 5%, showing that Orca-T treatment had limited serious adverse effects [45].

Discussion

Relapse of acute myeloid leukemia (AML) post allogeneic hematopoietic cell transplantation (allo-HCT) poses significant challenges distinct from relapse in non-transplant settings, primarily due to potential complications like graft-versus-host disease (GVHD) and the absence of randomized trials for guidance. Effective management often hinges on early intervention upon detection of falling donor chimerism or recurring leukemia-defining mutations suggestive of measurable residual disease (MRD). While the focus of this review is predominantly on strategies for handling overt morphologic relapse, attention to patients experiencing ongoing GVHD-related complications at relapse is crucial. Such cases demand simultaneous GVHD management, which can constrain treatment options and preclude participation in clinical trials due to heightened risks. For those with active GVHD, targeted therapies against specific mutations like FLT3, IDH1, and IDH2 may be viable, as evidence suggests minimal impact on GVHD exacerbation. Control of GVHD permits consideration of lower-intensity therapies such as azacitidine, decitabine, or azacitidine/venetoclax for individuals lacking targetable mutations or unresponsive to targeted treatments. However, responses to these approaches are typically transient, necessitating subsequent consideration of cellular immunotherapy with donor lymphocyte infusion (DLI) or a second allogeneic transplant. Yet, caution is warranted, as a history of moderate to severe acute GVHD before a second transplant or DLI substantially heightens the risk of non-relapse mortality and diminishes overall survival.

In post-transplant AML relapse without ongoing GVHD complications, treatment often starts with discontinuing immunosuppression but requires additional interventions for effectiveness. While direct comparisons are scarce, FLT3, IDH1, and IDH2 inhibitors show promising response rates with reduced toxicity, favoring targeted therapy for mutation-positive cases. Factors like age and disease aggressiveness guide the choice between intensive and lower-intensity therapies. Subsequent cellular immunotherapy with DLI or a second transplant should be considered upon achieving a response, as durable responses without it are uncertain. Despite persistent leukemia, DLI or a second transplant may be considered for fit patients, albeit with careful consideration of risks. Novel agents, including targeted therapies and immunotherapies, offer potential in augmenting the graft-versus-leukemia effect. Further research is crucial given the increasing post-transplant relapse rates for AML. Insights into immunological mechanisms may inform tailored treatment strategies, thereby enhancing outcomes.

Table 1

Therapy	Outcome	References
Donor lymphocyte infusion	- Induces remission in post-allo-HCT patients with CML who relapse- Potentially increases survival in patients with prior haploidentical transplant- Important to understand the consequences of DLI to determine suitable candidates	- 7, 43
Hypomethylating agents	- Maintenance therapy post allo-HCT remains controversial and unclear.- Potential prophylactic use due to tolerability.	- 12, 38
Targeted therapy	- Ivosidenib: Promising results, needs further investigation post-transplant. - Olutasidenib: Early study results are promising; longer-term studies needed.- Enasidenib: 35% overall response rate post-relapse allo HCT, potential standalone agent.- Sorafenib: Option for very poor risk FLT3 ITD-mutated AML patients post allo-BMT relapse.- Gilteritinib: Improved response rate (36% vs 18%) in post-allo-HCT patients; basis for treatment in FLT3-positive AML post-transplant.- Quizartinib: Antitumor activity in FLT3-positive AML; use as a single agent post-allotransplant relapse remains to be demonstrated.- Crenolanib: Improvement over other treatments not known; phase 3 trial terminated.	- 17, 44, 18, 39, 40, 20, 21, 22
Immunotherapy	- Ipilimumab and Nivolumab: Adverse events expected; need strategies to reduce toxicity while maximizing efficacy.- Gemtuzumab: Safe profile, another option for post-allo-HCT relapse.- Flotetuzumab: Early results encouraging; further investigations needed.- CAR T: Shows promise, revolutionary in ALL treatment, needs more studies with larger populations.- Orca-T: 81% relapse-free survival at 1 year and 18 months in AML patients; low rates of greater than grade 3 GVHD (5%).	- 26, 27, 28, 41, 34, 37, 45

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