

# Prophylaxis and treatment of acute lymphoblastic leukemia relapse after allogeneic hematopoietic stem cell transplantation

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**Abstract:** Relapse of acute lymphoblastic leukemia remains a major cause of death in patients following allogeneic hematopoietic stem cell transplantation. Several factors may affect the concurrence and outcome of relapse, which include graft-versus-host disease, minimal residual disease or intrinsic factors of the disease, and transplantation characteristics. The mainstay of relapse prevention and treatment is donor leukocyte infusions, targeted therapies, second transplantation, and other novel therapies. In this review, we mainly focus on addressing the impact of graft-versus-host disease on relapse and the prophylaxis and treatment of acute lymphoblastic leukemia relapse following allogeneic hematopoietic stem cell transplantation. We also make recommendations for critical strategies to prevent relapse after transplantation and challenges that must be addressed to ensure success.

**Keywords:** acute lymphoblastic leukemia, relapse, allogeneic hematopoietic stem cell transplantation, prevention, therapy

## Introduction

Relapse of acute lymphoblastic leukemia (ALL) after allogeneic hematopoietic stem cell transplantation (allo-HSCT) remains a significant therapeutic challenge, especially for adult ALL.<sup>1</sup> For patients with ALL who relapse after allo-HSCT, the treatment options are limited and the clinical course and prognostic factors affecting outcome have not been well characterized.<sup>2,3</sup> Although a better understanding of the graft-versus-tumor/graft-versus-leukemia (GVL) effect,<sup>4</sup> minimal residual disease (MRD), and donor leukocyte infusions (DLIs)<sup>5</sup> have been achieved in recent decades, predicting ALL relapse after allo-HSCT and finding strategies to overcome ALL relapse remain critical to clinical practitioners. The aim of this article is to review the current concepts regarding risk factors, prevention, and treatment of ALL relapse following allo-HSCT.

## Graft-versus-host disease and its impact on relapse

Numerous reports have demonstrated that graft-versus-host disease (GVHD) is associated with patient relapse after transplantation.<sup>6-10</sup> In ALL, a potent GVL effect is recognized,<sup>1</sup> and finding methods to trigger a more potent GVL response without increasing the risk of GVHD is the ultimate goal of HSCT.<sup>11</sup> However, clinical evidence also suggests that there may be protective GVL effects associated with mild or moderate GVHD.<sup>12,13</sup> In order to examine whether GVHD is associated with a GVL effect that influences the outcome of allo-HSCT in childhood ALL, Gustafsson Jernberg et al<sup>7</sup> examined 112 ALL patients and found that

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chronic GVHD independently decreased the risk of relapse (relative risk [RR] 0.44) and further predicted an increased chance of relapse-free survival (RR 1.7) and survival (RR 2.6). The impact of chronic GVHD on survival was most apparent in late-stage ALL. However, acute GVHD was not an independent predictor for relapse or mortality. This study is in support of a GVL effect in childhood leukemia related to chronic GVHD, reducing the risk of relapse and improving survival.

In a recent clinical trial by Chen et al<sup>14</sup> data from 18 patients with ALL who underwent allo-HSCT over the previous 12 years were collated, and they found that high-risk ALL and lack of chronic GVHD were risk factors for relapse (all  $P < 0.05$ ). Another study, by Lee et al<sup>15</sup> focused on adults with ALL who received myeloablative allo-HSCT from a matched sibling or unrelated donor and demonstrated that chronic GVHD, especially the limited type, has a significant antileukemic effect. It was also found that the influence of chronic GVHD on relapse risk was prominent in patients with chromosomal translocations or normal cytogenetics. The positive influence of chronic GVHD on survival rates in ALL patients is also confirmed in several other clinical studies.<sup>9,16,17</sup> However, the exact mechanisms of this GVL effect are poorly understood at present. Chronic GVHD is an autoimmune syndrome driven by diverse immune processes; thus, the relationship between chronic GVHD and graft-versus-tumor disease needs further analysis and understanding, and may help identify new therapies in the future.

## Minimal residual disease and relapse

Patients with MRD prior to transplantation are more likely to respond positively, and MRD is shown to have a strong correlation with cases of post-transplant relapse.<sup>18</sup>

## MRD monitoring before and after transplantation

Monitoring MRD before and after transplantation would allow doctors to assess a patient's prognosis more effectively and prevent potential relapse.<sup>19,20</sup> Emerging tools used for monitoring MRD and chimerism could predict patients at highest risk for relapse and provide us with an opportunity to pre-empt and mitigate relapse severity. Patients with increasing chimerism or MRD have been shown to benefit from early withdrawal of immune suppression or donor lymphocyte infusion.<sup>21</sup> Traditionally, polymerase chain reaction is a way of monitoring for MRD, especially in children. Nowadays, the use of high-throughput sequencing-based MRD monitoring in adults with ALL offers a standardized

approach to quantify leukemia MRD in peripheral blood.<sup>22</sup> Monitoring of MRD by four-color multiparametric flow cytometry could also be a key pre-emptive intervention.<sup>23</sup>

## MRD as a prognostic factor for relapse following transplantation

Several studies have demonstrated that patients at intermediate risk of relapse with low MRD can be considered to have a good prognosis.<sup>24–26</sup> This was confirmed by Balduzzi et al<sup>26</sup> in a study in which 82 children and adolescents underwent allo-HSCT for ALL in remission (period 2001–2011, median follow-up 4 to 9 years). Similarly, Terwey et al<sup>25</sup> performed a retrospective analysis of serial chimerism assessments in 101 adult HSCT recipients with ALL and of serial MRD assessments in a subgroup of 22 patients, all of whom had received myeloablative conditioning. Patients with higher MRD values after HSCT had the highest incidence of relapse among all the prognostic groups analyzed. In another study by Uzunel et al<sup>27</sup> MRD assessments were performed retrospectively after allo-HSCT in 32 patients with ALL (23 children and nine adults). Using immunoglobulin and T-cell receptor rearrangements as clonal markers, MRD was detected after allo-HSCT in nine patients, eight of whom have relapsed. This research has demonstrated that MRD status after induction therapy is one of the most significant prognostic factors. Leung et al<sup>28</sup> evaluated 64 children with very-high-risk ALL, and found that higher MRD levels at the time of HSCT predicted poor survival after HSCT ( $P = 0.0019$ ) and that MRD was an independent prognostic factor in multivariate analysis ( $P = 0.0035$ ). A retrospective cohort study by Shah et al of children with acute leukemia or myelodysplastic syndrome who had undergone their first allogeneic transplantation also demonstrated that MRD alone does not adequately predict relapse in all patients, and that MRD positivity was only an independent risk factor predictive of relapse.<sup>29</sup>

## Intervening in relapse based on MRD

Using immune or molecular techniques to establish MRD then using this metric to intervene before relapse occurs has been shown to be feasible. Risk stratification-directed intervention with modified DLIs in patients with standard-risk ALL who are MRD-positive following transplantation could improve transplantation outcomes.<sup>30</sup>

## Conflict of the relationship between MRD and ALL

A recent retrospective cohort analysis of children with acute leukemia after transplantation by Shah et al<sup>31</sup> suggested that

there was no improved survival in those patients whose leukemia was detected in a state of MRD post transplantation. This indicates that the relationship between MRD and ALL relapse might be more complex than we thought, and other significant factors may need to be investigated before drawing conclusions regarding the exclusivity of using MRD alone as a metric for prediction of post-allo-HSCT relapse.

## Major risk factors affecting relapse after allo-HSCT

Given the importance of pre-existing risk factors in predicting post-transplantation ALL relapse, there has been significant effort devoted to elucidating the value of individual and combined factors in patient outcomes (Table 1).

### Disease and disease status

Intrinsic factors of the disease play an important role in ALL relapse. Besides cytogenetics, many patient disease-related and treatment-related factors have been recognized that serve as predictors for outcome, such as age (risk of relapse increases with age), comorbidities, and disparities in human leukocyte antigen (HLA).<sup>32,33</sup> Factors predicting ALL relapse following allo-HSCT include a high white blood cell level at diagnosis, adverse cytogenetics, a mature B phenotype, and short initial remission.<sup>17,34</sup> In various clinical trials, sex, age, absence of chronic GVHD for more than 6 weeks from the time of diagnosis to complete remission (CR), active disease at the time of first HSCT along with short time to progression from first HSCT (less than 6 months), and low levels of interleukin-12 post HSCT are also risk factors for relapse after transplantation.<sup>17,35-42</sup>

### Gene expression

Several studies suggest that the expression of particular genes is associated with relapse in patients. In a clinical trial by Gandemer et al,<sup>35</sup> ETV6/RUNX1 expression were examined in 713 ALL childhood patients and it was found that increased expression was a strong indicator of overall survival post relapse. Another study by Liu et al<sup>43</sup> concluded that expression of the mixed lineage leukemia gene in ALL patients may indicate a higher risk of relapse after allo-HSCT. In a study by Krentz et al<sup>24</sup> IKZF1 deletion and TP53 mutation were also found to increase the risk after relapse in 204 children treated uniformly for B-cell precursor ALL, and this was confirmed in a clinical trial conducted by Beldjord et al.<sup>44</sup> Similarly, a high vascular endothelial growth factor-A level, NOTCH1/FBW7 mutations, NOD2/CARD15 genotypes, activating STAT5B N642H mutation, and CD19 were demonstrated to coincide with relapse after allo-HSCT treatment.<sup>45-50</sup>

### Transplant characteristics

Protection against relapse can be increased using unrelated donors, cord blood donors, or HLA-matched donors.<sup>17,37,40,51</sup> To improve outcomes and decrease the risk of relapse, younger donors should also be sought.<sup>52</sup>

### Prophylaxis against relapse after allo-HSCT

Patient survival is greatest when relapse does not occur post-allo-HSCT, so early detection of relapse and prediction of relapse based on contributing factors is the best approach for overall patient survival.<sup>32</sup> Based on previous data, we provide

**Table 1** Risk factors of acute lymphoblastic leukemia relapse and associations

Risk factors	Relapse association
<b>Disease and disease status</b>	
Age	High relapse with advancing age
Sex	High relapse within females
Phenotype	High relapse with a mature B phenotype
Cytogenetics	High relapse: t(9; 22), t(4; 11), t(1; 19), t(17; 19), t(5; 14), -7, +8, del(7p), complex ( $\geq 5$ abnormalities), hypodiploidy, triploidy, MLL translocation
MRD	High relapse with detection at various time-specific points
Chronic GVHD	High relapse with the absence of chronic GVHD
<b>Transplantation</b>	
	High relapse: short initial remission, >6 weeks from the diagnosis to CR, active disease at the time of first HSCT and short time to progression from first HSCT
	Low relapse: young, alternative, unrelated, cord blood donors or HLA-matched donors
<b>Gene expression</b>	
	High relapse: MLL expression, IKZF1 deletion, TP53 mutation, FBW7 mutation, STAT5B N642H, BCR-ABL1 rearrangements, and CD19
	Low relapse: ETV6/RUNX1 expression

**Abbreviations:** CR, complete remission; GVHD, graft-versus-host disease; HLA, human leukocyte antigen; HSCT, hematopoietic stem cell transplantation; MRD, minimal residual disease; MLL, mixed lineage leukemia.

our recommendations for critical strategies to prevent relapse after transplantation.

## Donor lymphocyte infusion

The GVL effect in ALL is probably one of the most potent strategies with curative potential, and DLI is an attractive option for prophylaxis against relapse of ALL after transplantation.<sup>14</sup> In a retrospective study by Wang et al<sup>53</sup> 88 patients with advanced-stage acute leukemia were treated with prophylactic granulocyte colony stimulating factor-primed peripheral blood stem cells (GPBPCI). The results showed that GPBPCI may increase survival in patients with advanced-stage acute leukemia who receive HLA-mismatched/haploidentical HSCT. A single-center prospective study also demonstrated that patients with ALL who received low-dose prophylactic DLI after conditioning with alemtuzumab were at low risk for relapse;<sup>54</sup> in addition, it was also shown that DLI should be used as early as possible.<sup>14</sup> However, the specific mechanism of the role of DLI in relapse still requires further investigation.

## Modulation of immunosuppression

Modulation of immunosuppression may reduce relapse risk and improve ultimate outcome.<sup>26</sup> Immunomodulatory regimens were also shown to induce moderate GVHD, and to enhance the GVL effect if implemented as soon as possible.<sup>14</sup>

## Targeted drugs

Administration of imatinib early after allo-HSCT could be an effective approach for preventing recurrent Ph+ ALL.<sup>55–57</sup> Pretransplant imatinib improved both relapse and non-relapse mortality in patients with BCR-ABL-positive ALL according to a recent multicenter clinical trial.<sup>58</sup> However, the patients experienced some adverse events related to administration of imatinib, such as grade 1–3 nausea, emesis, and serum transaminase elevations.<sup>55,56</sup> Recently, romidepsin, an anti-cancer agent undergoing clinical trials, has also been demonstrating utility for patients with relapsed ALL.<sup>59</sup>

## Cytokines

Interleukin-2, a very-well-characterized T-cell growth factor, has also been administered to patients with ALL for relapse prophylaxis.<sup>1,60</sup> Liu et al<sup>61</sup> studied 19 patients with ALL who underwent interleukin-2 treatment for a high probability of disease recurrence after allo-HSCT. They found that low-dose interleukin-2 could be a safe and effective strategy to prevent relapse in ALL patients with a high risk of recurrence

after unmodified allo-HSCT. The side effects of this treatment consisted primarily of fever, pain, redness, and swelling at the injection site.

## Targeting genes related to relapse

Some genes are associated with the occurrence of ALL relapse. Targeting these mutated genes with specific treatments may be a possible strategy to prevent relapse.<sup>11</sup> Several clinical trials have attempted targeting therapy and had good outcomes. For example, Cooke et al<sup>62</sup> discovered that targeting the mixed lineage leukemia-AF4 oncogene could inhibit cell proliferation in human ALL, and inhibiting the Wnt pathway also demonstrated a positive outcome in ALL.<sup>63,64</sup>

## Strategies and treatment options for relapsed ALL following allo-HSCT

For relapsed ALL, measures such as DLI, optimized chemotherapy regimens, second transplantation, novel agents, tumor vaccines, and monoclonal antibodies may lead to improvement in survival rates.

## Donor lymphocyte infusion

Among the different therapeutic options, DLIs are probably the most consolidated strategy but their efficacy is quite variable depending on disease state.<sup>65–67</sup> Very few ALL patients benefit from DLIs because of GVHD. The occurrence of acute GVHD is affected by the degree of HLA matching and the type of donor. The development of chronic GVHD after DLIs is associated with the highest rate of response to DLI and higher survival rates.<sup>68</sup>

Replacing steady-state lymphocytes with peripheral blood grafts (G-PB) and applying a short course of an immunosuppressive agent can reduce the incidence of DLI-associated acute GVHD without affecting relapse or survival of patients with hematological disease after receiving allo-HSCT.<sup>11</sup> In a study by Zhao et al of 194 patients undergoing allo-HSCT, the patients received mobilized DLI for various clinical reasons and the results showed that infusion with a dose of CD14-positive cells at greater than the 50th percentile was associated with a lower incidence of hematological relapse and longer disease-free survival after mobilized DLI.<sup>5</sup>

However, because of the low likelihood of achieving a durable CR, DLI is not considered standard for patients with relapsed ALL after allo-HSCT.<sup>8</sup> This has led to further investigation of other forms of adoptive cellular therapies post-allo-HSCT.

## Chemotherapy

Post-transplantation patients who have relapsed may obtain positive results from chemotherapy. However, the major function of chemotherapy is to decrease tumor load, hence chemotherapy should be combined with other therapeutic treatments for greater effect. A recent study showed that patients with relapsed-refractory ALL treated with fludarabine, cytarabine, and liposomal daunorubicin (FLAD), followed by HSCT, had a better prognosis and less frequent relapse. Thus, FLAD appears to be an effective bridge therapy to HSCT for a subset of acute leukemia patients with a poor prognosis.<sup>69</sup> Although promising, this treatment regime still needs further investigation to determine its overall effectiveness.

## Second transplantation

The efficacy of second transplantation is mainly affected by disease status, duration from relapse to the first transplantation, previous chemotherapy, and the general condition of the patient. A second transplant is one of the few treatment options that provides the possibility for long-term survival in relapsed ALL patients after allo-HSCT, and there are some successful reports.<sup>8,70</sup>

## Targeted therapies

Imatinib is a targeted drug that can be used to treat Ph+ ALL patients. Several studies have demonstrated that post-transplant administration of imatinib is an ideal treatment for Ph+ ALL patients, and post-transplant imatinib has also been demonstrated to result in lower relapse rates.<sup>71,72</sup> However, in a retrospective clinical trial that included 34 Ph+ ALL patients, the researchers discovered that post-transplant administration of imatinib is not an ideal treatment for Ph+ ALL patients whose MRD is positive at allo-HSCT.<sup>72</sup> Reappearance of BCR-ABL1 transcripts early after HSCT or at higher levels also identifies a small subset of patients who do not benefit sufficiently from imatinib.<sup>71</sup> Dasatinib, a novel ABL tyrosine kinase inhibitor, was found to have excellent efficacy in Ph+ ALL in a recent study.<sup>73</sup> Dasatinib could also eradicate MRD and prevent recurrence, so it has advantages over imatinib, but further studies are needed to confirm its effects.

## Tumor vaccines

A variety of leukemia-associated antigens have been utilized in novel tumor vaccines. Dendritic cells and artificial antigen-presenting cells can be utilized in tumor vaccines to improve the immune response to tumor-associated

antigens.<sup>74–76</sup> Continued advances in tumor immunology and immunotherapy may facilitate the application of these approaches to the treatment of relapsed ALL after allo-HSCT in the future.

## Monoclonal antibodies

Multiple monoclonal antibody-based reagents that target ALL-associated surface antigens have been developed and are under investigation at present.<sup>77–80</sup> The use of monoclonal antibodies that target tumor-associated antigens would be useful for treating ALL relapse after allo-HSCT, but this still needs further research.

## Conclusion

Despite outstanding advances in our knowledge of ALL in the past three decades, relapsed ALL following an allo-HSCT has a dismal prognosis. Outcomes are particularly poor for patients with relapsed ALL, and overall survival rates are less than 15%.<sup>56</sup> Better understanding of GVL/GVHD and monitoring MRD before and after transplantation may be helpful for clinicians to determine the best treatment options on a patient-by-patient basis. The prevention and treatment strategies for relapse of ALL after allo-HSCT continue to evolve, with advancing developments using a variety of novel approaches. It is clear that critical information regarding both the progress and prognosis of a patient can be gleaned from every stage of treatment, and when properly interpreted can significantly improve survivability. We are confident that with advances in conditioning regimens, vaccines, graft engineering, and epigenetic modifiers, there is a future ahead with significantly less rate of relapse in ALL after allo-HSCT.

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## Disclosure

The authors report that they have no conflicts of interest in this work.

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