

# Management of pediatric acute leukemias relapse after hematopoietic cell transplantation

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## ABSTRACT

Prevention is the best way to avoid relapse after hematopoietic cell transplantation (HCT). Immunomodulation can enhance graft-versus-leukemia effect and, if graft-versus-host disease (GVHD) is absent, prophylactic donor lymphocyte infusion (DLI) may be indicated for high-risk patients. Maintenance strategies with blinatumomab, inotuzumab, tyrosine kinase inhibitors, hypomethylating agents or venetoclax can be effective in reducing relapse rates. However, maintenance therapy response depends on individual toxicity and physician's experience in handle with dose adjustments, undesirable drug interactions and complications. Preemptive approach guided by minimal residual disease (MRD) or mixed chimerism is fundamental to prevent hematologic relapse. Target agent or immunotherapy followed by DLI can be used, and if no response, low-dose chemotherapy can be added to reach disease control. After relapse, antigen-directed therapies with blinatumumab for CD19 ALL and inotuzumab for CD22 ALL are good options to induce MRD negativity and bridge to second HCT. Emerging therapies like daratumumab, immune checkpoint or menin inhibitors are promising but require validation. CAR-T cell therapy can provide a better chance of long-term survival if low leukemia burden and absence of GVHD. It is also effective in extramedullary disease, mainly in central nervous system relapse. Patients with B-cell aplasia loss after CART-cell therapy are second transplant candidates, as well as those with acute myeloid leukemia who respond to salvage therapy. Second HCT outcomes are better if relapse occurred  $\geq 12$  months after the first HCT. Strategies for expanding access to immunotherapy and target agents are crucial to improve long-term survival in these children.

**Keywords:** Leukemia. Neoplasm, Residual. Chimerism. Maintenance.

## INTRODUCTION

Relapse remains the primary cause of post-hematopoietic cell transplantation (HCT) treatment failure. In Brazil, access to advanced therapies is limited, making prevention strategies crucial. Several key risk factors have been identified, including refractory disease, disease status beyond first remission, positive minimal residual disease (MRD) pre-HCT, and mixed donor chimerism<sup>1</sup>. A Brazilian study of outcomes after unrelated donors or umbilical cord blood HCT for pediatric leukemia showed a three-year relapse rate of 23%, but relapse was the main cause of deaths (36%) in this cohort<sup>2</sup>.

Pediatric prevention strategies are typically extrapolated from adult studies due to limited research. Post-HCT maintenance therapy should target high-risk patients: those with refractory disease, MRD+, high-risk cytogenetics, and diseases with molecular targets or lacking salvage options. Epstein-Barr virus-associated post-transplant lymphoproliferative disorders (PTLD) treatment was associated with higher relapse rates, making these patients strong candidates for post-transplant maintenance therapy<sup>3</sup>.

Most relapses occur in three to six months post-HCT, requiring early intervention. Maintenance should begin after graft stabilization and resolution of early complications. In the absence of graft-versus-host disease (GVHD) at day 60, immunosuppression tapering can start, with complete discontinuation between day 90–120. Despite upfront costs, maintenance proves more cost-effective than relapse treatments. Comprehensive monitoring remains essential, and previous drug refractoriness should guide therapy selection. Leukemia subtype-specific approaches are outlined in Table 1.

**Table 1.** Suggested maintenance strategies, according to the leukemia subtype.

| Disease       | Drug                                                                                 | Indications                                                                                                                                                                                                                                 | Dose                                                                                                                                                                            | Expected toxicities/monitoring                                                                                                                                                                                       | Suggested duration                                                                                            |
|---------------|--------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------|
| B-ALL         | Blinatumomab (± donor lymphocyte infusion) <sup>4-7</sup>                            | Highest risk, pre- and/or post-HCT CD19+ MRD                                                                                                                                                                                                | 15 mcg/m <sup>2</sup> /day IVC for 28 days                                                                                                                                      | Cytopenias, fever in the first days of the first and second cycles                                                                                                                                                   | Two to five cycles (interval 0.5–three months)                                                                |
|               | Inotuzumab ozogamicin <sup>8</sup>                                                   | Highest risk, and/or post-HCT CD19 neg CD22+ MRD; disease refractory to blinatumomab                                                                                                                                                        | 0.3–0.6 mg/m <sup>2</sup>                                                                                                                                                       | Thrombocytopenia; avoid if prior sinusoidal obstruction syndrome                                                                                                                                                     | Four to eight monthly cycles                                                                                  |
| Ph+ B-ALL     | Imatinib (or active TKI prior to HCT or based on patient's mutation) <sup>9,10</sup> | All Ph+ ALL, if BCR-ABL+ before or after HCT. Individualize the decision between prophylactic or preemptive use.<br>Prophylactic: for patients with +MRD pre-HCT or ≥ CR2 or BCR-ABL kinase mutation.<br>Preemptive: for patients with GVHD | Imatinib: 260 mg/m <sup>2</sup> increased up to 300 mg/m <sup>2</sup> if tolerated. If there is no response to the inhibitor, perform mutation testing and switch the inhibitor | Avoid TKI with prior severe toxicities; cardiovascular complications; cytopenias. If there is intolerance, consider changing the inhibitor. In cases involving central nervous system, dasatinib is the first choice | At least one or two years.<br>If preemptive approach: 2 years from first MRD negative or chimerism conversion |
| T-ALL         | Azacitidine + venetoclax <sup>11,12</sup>                                            | Highest-risk T-ALL patients, previously refractory or MRD+ prior to HCT                                                                                                                                                                     | AZA: 32 mg/m <sup>2</sup> for five days in 28-day cycles<br>Venetoclax: 100 mg/m <sup>2</sup> for 7–14 days starting with AZA, adjusted according to cytopenias                 | Myelosuppression, mild GI symptoms                                                                                                                                                                                   | AZA: six cycles<br><br>One year of venetoclax                                                                 |
|               | Azacitidine <sup>13</sup>                                                            | High-risk AML without targetable mutations                                                                                                                                                                                                  | 32 mg/m <sup>2</sup> for five days in 28-day cycles                                                                                                                             | Myelosuppression                                                                                                                                                                                                     | 6–12 cycles (every 28 days)                                                                                   |
| AML           | Decitabine + G-CSF <sup>14</sup>                                                     | Alternative to AZA in patients with low blood counts                                                                                                                                                                                        | Decitabine: 5 mg/m <sup>2</sup> D1–D5 every between six and eight weeks; G-CSF: 100 mg/m <sup>2</sup> D0–D5                                                                     | Myelosuppression                                                                                                                                                                                                     | Six cycles (every six to eight weeks)                                                                         |
|               | Venetoclax <sup>15–17</sup>                                                          | Alternative to AZA/decitabine                                                                                                                                                                                                               | 100 mg/m <sup>2</sup> for 7–14 days, monthly cycles adjusted if myelosuppression                                                                                                | Myelosuppression<br>Mild GI symptoms                                                                                                                                                                                 | One year                                                                                                      |
| FLT3 ITD+ AML | Sorafenib <sup>18,19</sup>                                                           | All FLT3+ AML                                                                                                                                                                                                                               | 100–200 mg/m <sup>2</sup> /day                                                                                                                                                  | Myelosuppression, cardiovascular, diarrhea                                                                                                                                                                           | One year                                                                                                      |
|               | Gilteritinib <sup>20</sup>                                                           | NGS+ MRD pre- or post-HCT                                                                                                                                                                                                                   | 2 mg/kg (maximum 120 mg/day), adjusted for tolerance                                                                                                                            | Myelosuppression, liver toxicity                                                                                                                                                                                     | One year                                                                                                      |

Source: Elaborated by the authors. ALL: acute lymphoblastic leukemia; AML: acute myeloid leukemia; TKI: tyrosine kinase inhibitor; HCT: hematopoietic cell transplantation; MRD: minimal residual disease; GVHD: graft-versus-host disease; AZA: azacitidine; NGS: next-generation sequencing; IVC: intravenous continuous; GI: gastrointestinal; Ph+: Philadelphia chromosome positive; CR: complete remission.

## MONITORING MINIMAL RESIDUAL DISEASE IN ACUTE LEUKEMIAS AFTER TRANSPLANTATION

MRD monitoring post-HCT is essential for detecting relapse risk in acute leukemias<sup>19–23</sup>. Key methodologies include multiparameter flow cytometry, quantitative polymerase chain reaction (qPCR), and next-generation sequencing. Standard assessments should be performed at specific time points: days 30, 60, 90, 180, and 365 post-transplant<sup>24</sup>. High-risk (positive MRD pre-transplant, aggressive disease, genetic alterations with poor prognosis) or MRD-positive patients require additional evaluation at day +270 and 18 months<sup>25</sup>. For acute lymphoblastic leukemia (ALL), combined qPCR and donor chimerism monitoring optimizes relapse prediction<sup>25</sup>. These techniques enhance therapeutic decisions through early intervention when tumor burden is low. Post-transplant MRD should be performed with centralized laboratory analysis to ensure standardization. However, evaluation timepoints may vary between centers, requiring individualized approaches based on institutional protocols and patient risk factors<sup>26–29</sup>.

## CHIMERISM AND MANAGEMENT OF MIXED CHIMERISM

Chimerism after allogeneic HCT is classified as complete donor (CC), mixed (MC), split, or absent as defined by the Brazilian Society of Bone Marrow Transplantation consensus<sup>30</sup>. MC can be stable, increasing, or decreasing<sup>31</sup>. Short tandem repeat-polymerase chain reaction (STR-PCR), with sensitivity around 1%, remains the main chimerism method, while CD34+ cells and leukemia-specific lineage analyses offer more accurate relapse prediction. Higher sensitivity techniques (0.01–1%) include digital PCR and NGS<sup>21</sup>.

### Monitoring schedule

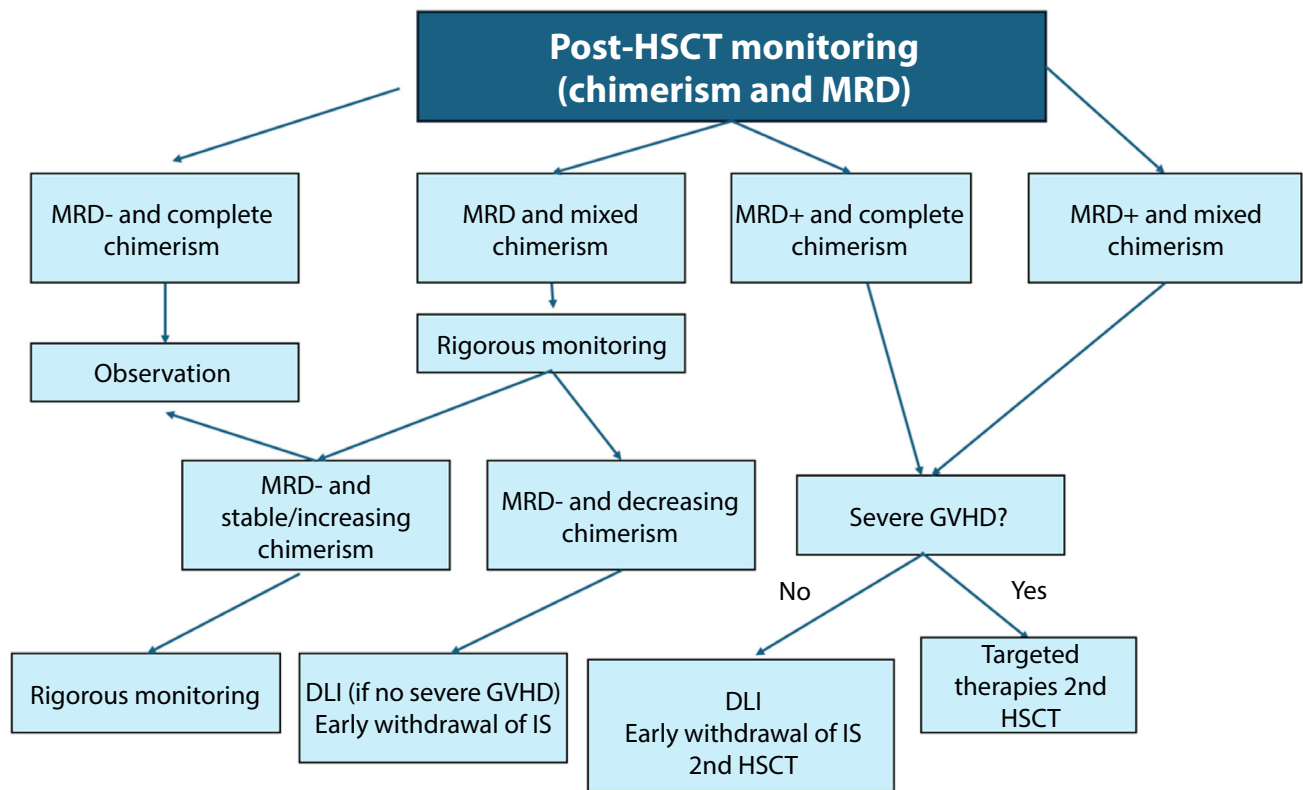
Perform chimerism collection (which can alternate between marrow/peripheral blood sources for each collection) according to clinical decision at the time, every two weeks until day 90, monthly in the first year and then annually until two years post-transplant at least. In some cases, collection may be evaluated at the following timings: 30, 60, 90, 180, 270 and 365 days post-transplant. Each case should be individually analyzed for clinical decision. Increase frequency if decreasing donor chimerism or persistent MC is detected<sup>24</sup>. Low-level chimerism (host cells < 1%) requires closer monitoring but not intervention. Sustained MC or early donor chimerism drop independently predicts relapse and impaired survival<sup>29</sup>. Interventions include rapid immunosuppression tapering with or without escalated donor lymphocyte infusions (DLIs). The DLI protocol recommends initial doses of  $1 \times 10^5$ – $10^6$  CD3+ cells/kg, increased by 0.5 log for subsequent doses, up to limits of  $10^7$  for matched unrelated donor and  $10^8$  for matched sibling donor<sup>32,33</sup>.

## DONOR LYMPHOCYTE INFUSION

DLI has been used for over 30 years to enhance the graft-versus-leukemia (GVL) effect following allogeneic HCT. Evidence demonstrates that prophylactic or preemptive DLI is more effective than therapeutic DLI administered after overt relapse. This approach helps convert mixed to complete donor chimerism and eliminates MRD. Adequate monitoring of chimerism and MRD are crucial in choosing prophylactic and therapeutic strategies (Fig. 1). Early intervention at low tumor burden substantially improves survival<sup>21</sup>. Recommendations of DLI strategies are summarized in Table 2.

### Key indications

- Prophylactic: *ex-vivo* T-cell depleted transplants, high-risk cytogenetics/molecular alterations, multiple treatment failures, pre-transplant MRD+,  $\geq$  CR2 or second transplant;
- Preemptive: increasing mixed chimerism, MRD positivity post-transplant (after immunosuppression withdrawal for  $\geq$  six weeks, beyond day +90, without GVHD signs);
- Other uses: delayed immune recovery, consolidation for hematological extramedullary relapses, PTLD treatment or prophylactic after rituximab use<sup>3,34</sup>;



Source: based on Miura et al.<sup>21</sup>. MRD: minimal residual disease; HSCT: hematopoietic stem cell transplantation; GVHD: graft-versus-host disease; DLI: donor lymphocyte infusion; IS: immunosuppression.

**Figure 1.** Interventions based on chimerism analysis and minimal residual disease after allogeneic hematopoietic cell transplantation for leukemia.

**Table 2.** Donor lymphocyte infusion strategies, according to indications, donor type, and time after hematopoietic cell transplantation<sup>34–37</sup>.

| Strategy          | Indications                                                                                                                                                        | First dose DLI (CD3/kg of weight)                                                                                                                                                                 |
|-------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Prophylactic DLI  | Standard:<br>- high risk at diagnosis;<br>- advanced or refractory disease at HCT (T-depletion ex-vivo)<br>Optional:<br>- RIC or NMA;<br>- absence of target drugs | 3 m: MSD/MUD / HAPLO: $1 \times 10^5$ ;<br>6 m: MUD/MSD: $1 \times 10^6$ ; HAPLO: $5 \times 10^5$ one to three doses with 0.5-log increase for both timepoints                                    |
| Pre-emptive DLI   | Standard:<br>- MC or +MRD;<br>- Molecular or cytogenetic relapse<br>Optional:<br>- Infections/ previous rituximab use                                              | 3 m: MSD $1-5 \times 10^5$ ; MUD and HAPLO: $1 \times 10^5$ ; one to four doses.<br>6 m: MUD/MSD: $1-3 \times 10^6$ ; MUD: $1 \times 10^6$ ; HAPLO: $5 \times 10^5$ ; one to four doses           |
| Therapeutic DLI   | Standard: hematological and extramedullary relapses<br>Optional: post-transplant lymphoproliferative disorders                                                     | After systemic therapy:<br>MSD and MUD $1 \times 10^7$ ; HAPLO: $1 \times 10^6$ ; one to four doses (every four to six weeks), with increase of up to 1 log (maximum total dose $1 \times 10^8$ ) |
| G-DLI + CSA       | Advanced or refractory disease at HCT. Contraindicated with any sign of GVHD                                                                                       | D+21 ( $10^6$ ); D+35 and D+60 ( $5 \times 10^6$ );<br>CSA tapering (four weeks) from D+60                                                                                                        |
| Fresh DLI from PB | Pro and pre-emptive (MC or MRD+); lack of access for apheresis; child donors; volume depends on CD3 count                                                          | MSD/MUD: $1 \times 10^5$ ;<br>HAPLO: $1 \times 10^4$ ; one to three doses escalating 0.5-log in each                                                                                              |

Source: adapted from Pagliuca et al.<sup>35</sup>. DLI: donor lymphocyte infusion; G-DLI: granulocyte colony-stimulating factor mobilized donor lymphocyte infusion; CSA: cyclosporine A; PB: peripheral blood; HCT: hematopoietic cell transplantation; RIC: reduced intensity conditioning; NMA: non-myeloablative conditioning; MC: mixed chimerism; MRD: minimal residual disease; GVHD: graft-versus-host disease; MSD: matched sibling donor; MUD: matched unrelated donor; HAPLO: haploidentical donor.

- Contraindications: active acute/chronic GVHD (absolute); previous cortico-sensitive aGVHD II-IV or moderate-severe cGVHD (relative). For high-progression risk, consider single low-dose DLI with azacytidine, but avoid immune-modulating drugs due to severe GVHD risk<sup>35</sup>. DLI is ineffective for relapses with HLA expression loss (30% of acute myeloid leukemia relapses)<sup>36–38</sup>;
- Complications: primary concerns include GVHD and cytopenia. Key GVHD risk factors are: mixed bone marrow chimerism (hazard *ratio*—HR = 3.63), reduced intensity conditioning for unrelated donor HCT (HR = 3.05), absolute lymphocyte count < 1,000×10<sup>6</sup>/L (HR = 2.05), and viral infections near DLI administration (HR = 3.66)<sup>39</sup>.

## ACUTE LYMPHOBLASTIC LEUKEMIA RELAPSE TREATMENT

Pediatric ALL relapse post-HCT has a poor prognosis, requiring individualized approaches based on relapse timing, prior therapy response, and therapeutic access<sup>40</sup>.

### Salvage chemotherapy options

- IDA-FLAG: achieves complete remission in a significant proportion with modest survival<sup>30,41</sup>;
- Bortezomib-based regimens limited efficacy; a Japanese phase-2 study showed no significant improvement. Still investigational for post-HCT relapse<sup>30,42</sup>;
- Nelarabine-based regimens are effective in relapsed/refractory T-cell ALL, with manageable toxicity<sup>43,44</sup>.

### Targeted therapies and immunotherapy

Targeted therapies have revolutionized treatment approaches for specific ALL subtypes, offering promising options for post-HSCT relapse:

- Tyrosine kinase inhibitors: essential for Ph+ ALL; options include dasatinib, nilotinib, and ponatinib; it can be combined with hyperCVAD, blinatumomab or DLI<sup>30,45,46</sup>;
- Inotuzumab ozogamicin (InO), CD22-directed antibody-drug conjugate; complete remission rates of 58.3%; dose: 1.8 mg/m<sup>2</sup>/cycle (fractionated), reduced to 1.5 mg/m<sup>2</sup>/cycle post-remission; risk of sinusoidal obstruction syndrome<sup>47–49</sup>;
- Blinatumomab, bispecific T-cell engager (CD19/CD3); complete remission in 48%, one-year survival of 40%; administered as four-week continuous infusion<sup>50,51</sup>;
- Daratumumab, anti-CD38 monoclonal antibody; promising for T-ALL (41.7% complete remission); dosing: 16 mg/kg IV weekly (cycles 1–2), then biweekly<sup>52,53</sup>;
- Venetoclax, CL-2 inhibitor; 61% complete remission in retrospective studies; weight-based dosing: 10–600 mg daily in 28-day cycles<sup>54–56</sup>;
- Emerging therapies: immune checkpoint inhibitors (pembrolizumab, nivolumab) and menin inhibitors for KMT2A-rearranged ALL show promise but require further validation<sup>57</sup>.

### CAR-T cell therapy in post-hematopoietic cell transplantation relapses

Effective for post-HCT relapses, particularly those occurring early<sup>58</sup>, CAR-T cell therapy in post-hematopoietic cell transplantation relapses shows efficacy in extramedullary recurrences, including central nervous system involvement<sup>59,60</sup>. Low GVHD incidence despite allogeneic origin in post-transplant patients<sup>61,62</sup>.

## ACUTE MYELOID LEUKEMIA RELAPSE TREATMENT

Relapse of acute myeloid leukemia (AML) following allogeneic HCT typically results from: resistance to prior chemotherapy, immune escape from GVL effect and high-risk biological factors (adverse genetic mutations). Prognostic factors include time to relapse, disease burden, patient age, clinical condition, and biological characteristics of the leukemia<sup>63–66</sup>. Main strategies and therapeutic options are described in Table 3.

**Table 3.** Main therapeutic options for management of acute myeloid leukemia relapse after hematopoietic cell transplantation.

| Strategy                                      | Therapeutic options                                                                                              | Key considerations                                                                                                                  |
|-----------------------------------------------|------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------|
| Chemotherapy <sup>4,64,67,68</sup>            | FLAG/IDA-FLAG protocols; venetoclax + HMA (decitabine, azacitidine)                                              | Emerging venetoclax combinations: promising efficacy and lower toxicity profile                                                     |
| Immunotherapy <sup>69–73</sup>                | Gemtuzumab ozogamicin (anti-CD33); CAR-T cell therapy; cytokine-induced memory-like NK cells                     | CAR-T approaches: still investigational<br>Various targets: good preliminary results                                                |
| Targeted therapy <sup>69,70,74,75</sup>       | FLT3 inhibitors; IDH1/IDH2 inhibitors; HDAC inhibitors; Selective inhibitors of nuclear export (XPO1 inhibitors) | Selection based on molecular profiling; IDH1/IDH2 inhibitors: good clinical efficacy in IDH-mutated acute myeloid leukemia patients |
| GVL modulation <sup>76,77</sup>               | Reduction of immunosuppression, donor lymphocyte infusion                                                        | Balance between GVL and GVHD risk; the timing of intervention is critical                                                           |
| Second transplantation <sup>65,66,78,79</sup> | Various conditioning regimens; consider TBI for central nervous system involvement                               | Significant toxicity and treatment-related mortality; Potentially curative; Careful patient selection                               |

Source: Elaborated by the authors. GVL: graft-versus-leukemia; HMA: hypomethylating agent; NK: natural killer; HDAC: histone deacetylase; TBI: total body irradiation; IDH: isocitrate dehydrogenase; GVHD: graft-versus-host disease.

### Treatment selection

Consider time since initial transplant, performance status, molecular profile, prior therapy response, and donor availability.

### EXTRAMEDULLARY RELAPSE IN PEDIATRIC LEUKEMIA POST-TRANSPLANTATION

Extramedullary relapse occurs in 5.5% of pediatric leukemia cases following allogeneic HCT<sup>80–82</sup>. Children are three times more likely than adults to develop extramedullary relapse post-transplant<sup>83</sup>.

### Risk factors

Younger age at transplant, prior extramedullary disease, advanced disease status (CR2+ or active disease), unfavorable cytogenetics, M4/M5 AML subtypes.

### Relapse sites

Central nervous system (most frequent), testicles, soft tissues, lymph nodes, skin, and myeloid sarcomas (particularly in AML)<sup>82,84</sup>.

### Differences between extramedullary and bone marrow relapses

In addition of specific risk factors, mechanism patterns, timing post-HCT, active GVHD presence, response to treatment and prognosis differ depending on the site of relapse<sup>82</sup>. Main differences are described in Table 4.

**Table 4.** Differences between extramedullary and bone marrow relapses.

| Characteristic     | Extramedullary relapse                     | Bone marrow relapse             |
|--------------------|--------------------------------------------|---------------------------------|
| Timing             | Later (10–17 months)                       | Earlier (three to seven months) |
| GVHD association   | More common (weaker GVL)                   | Less common                     |
| Immune mechanism   | Immune-mediated resistance                 | Less immune escape              |
| Treatment response | Poor DLI response but longer RFS           | Better immune therapy response  |
| Prognosis          | Better if isolated (> six months post-HCT) | Generally poorer                |

Source: Elaborated by the authors. GVHD: graft-versus-host disease; GVL: graft-versus-leukemia; DLI: donor lymphocyte infusion; RFS: relapse-free survival; HCT: hematopoietic cell transplantation.

## Diagnosis<sup>85</sup>

No standardized screening exists, often resulting in delayed detection. Fluorodeoxyglucose (FDG)-positron emission tomography/computed tomography is valuable for early identification, especially when combined with MRD monitoring.

## Treatment options

- Systemic chemotherapy: regimens with intrathecal therapy/radiotherapy<sup>80,86</sup>;
- DLI, though less effective in extramedullary relapse<sup>80,87</sup>;
- Second allogenic HCT: for patients with good performance status and salvage response<sup>86</sup>;
- Local radiotherapy, which does not prevent future extramedullary relapses;
- Hypomethylating agents potentially enhance GVL effect<sup>88</sup>.

Despite distinct biological and therapeutic challenges, allogenic HCT remains the best curative option for extramedullary relapses. Optimized monitoring and individualized treatment are crucial for improving outcomes.

## RESULTS AND PROGNOSTIC FACTORS OF A SECOND HEMATOPOIETIC CELL TRANSPLANTATION IN PEDIATRIC ACUTE LEUKEMIAS

For patients with post-first-HCT relapse, curative options are limited. Second HCT offers a promising alternative despite guarded prognosis, with recent data showing four-year overall survival (OS) of 31% for AML and three-year OS of 22.4% for ALL<sup>89</sup>. Identifying prognostic factors is essential for patient selection and outcome optimization<sup>90</sup>.

### Prognostic factors

- ALL: > 12 months between transplants, chronic GVHD after first HCT, remission pre-2nd HSCT and performance status > 80 (Lansky/Karnofsky);
- AML: > 12 months between transplants, chronic GVHD after first HCT, > 12 years of age and performance status > 80 (Lansky/Karnofsky)<sup>91</sup>.

No evidence supports replacing the original donor for the second procedure. Conditioning regimen selection requires assessment of the patient's current clinical status, previous comorbidities, and first transplant conditioning scheme. Common approaches include TBI-based or busulfan-based protocols. Post-CAR T-cell therapy patients with B-cell aplasia loss are candidates for second transplant. All cases require individualized evaluation due to unique clinical characteristics.

## CONCLUSION

Relapse after HCT remains the foremost challenge in pediatric acute leukemias, significantly impacting long-term survival. The Brazilian context makes prevention strategies particularly crucial for proper patient management. Prevention efforts should prioritize high-risk patients with refractory disease, positive MRD (pre/post-HCT), and unfavorable cytogenetics. Early intervention yields substantially better outcomes, with timely DLI serving as a cornerstone immunotherapeutic approach when implemented prophylactically or preemptively rather than after overt relapse. A comprehensive monitoring strategy tumor burden remains low.

Maintenance therapy, initiated early post-HCT, offers promising results for high-risk patients in preventing relapse. For patients who experience relapse despite preventive measures, treatment must be tailored based on disease characteristics, relapse timing, and prior therapy response. Novel therapies including targeted agents and immunotherapies have expanded the therapeutic arsenal. The heterogeneity of post-HCT relapse underscores the need for personalized approaches and multicenter collaboration to develop pediatric-specific protocols.

## CONFLICT OF INTEREST

Nothing to declare.

## DATA AVAILABILITY STATEMENT

All dataset are presented/analysed in the text.

## AUTHORS' CONTRIBUTIONS

**Substantive scientific and intellectual contributions to the study:** Tavares RCBS, Pelegrina PRD, Breviglieri CNM, Rodrigues ALM, Zamperlini G, Sousa AM, Horn PRCB and Daudt LE. **Conception and design:** Tavares RCBS, Pelegrina PRD, Breviglieri CNM, Rodrigues ALM, Zamperlini G, Sousa AM, Horn PRCB and Daudt LE. **Analysis and interpretation of data:** Tavares RCBS, Pelegrina PRD, Breviglieri CNM, Rodrigues ALM, Zamperlini G, Sousa AM, Horn PRCB and Daudt LE. **Manuscript writing:** Tavares RCBS, Pelegrina PRD, Breviglieri CNM, Rodrigues ALM, Zamperlini G, Sousa AM, Horn PRCB and Daudt LE. **Critical review:** Darrigo Júnior LG. **Final approval:** Tavares RCBS.

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## REFERENCES

1. Pelegrina PRD, Tavares RCB, Rodrigues AM, Loth G, Nichele S, Kuwahara C, Benini FML, Peixoto CMA, Bach J, Trennepohl J, de Gouveia LMM, Muratori R, Koliski A, Gomes RT, Quiroga M, Lermontov SP, da Silva VG, de Azambuja AP, Feitosa MK, Lima ACM, Bonfim C. Clinical outcomes and relapse patterns in pediatric acute leukemia patients undergoing hematopoietic cell transplantation: a multicenter Brazilian experience. *Front Pediatr.* 2025;13:1573334. <https://doi.org/10.3389/fped.2025.1573334>
2. Tavares RCB, Bonfim CS, Seber A, Pereira Lermontov S, Coulturato V, Zecchin VG, Ribeiro L, Fernandes JF, Daudt LE, Grecco CS, Darrigo-Jr. LG, Villela N, Nichele S, Gouveia R, Bouzas LF, Hamerschlak N, Vigorito AC, da Silva PM, da Silva PO, da Silva CC, de Souza Fernandez C, Flowers ME, Arcuri LJ. Hematopoietic cell transplantation in pediatric patients with acute leukemias or myelodysplastic syndrome using unrelated adult or umbilical cord blood donors in Brazil. *Pediatr Transplant.* 2020;24(7):e13789. <https://doi.org/10.1111/petr.13789>
3. Marjańska A, Pogorzała M, Dziedzic M, Czyżewski K, Richert-Przygońska M, Dębski R, Bogiel T, Styczynski J. Impact of prophylaxis with rituximab on EBV-related complications after allogeneic hematopoietic cell transplantation in children. *Front Immunol.* 2024;15:1427637. <https://doi.org/10.3389/fimmu.2024.1427637>
4. Breviglieri CNM, Gouveia RV, Ginani VC, Santos CN, de Oliveira MRS, Batalha ABW, de Alencar GS, Goto EH, Marques JF, Pupim MPV, Seber A. Post-stem cell transplant maintenance for pediatric acute leukemias: insights from a Brazilian institution with a Latin American perspective. *Front Oncol.* 2025;15:1540158. <https://doi.org/10.3389/fonc.2025.1540158>

5. Ueda M, de Lima M, Caimi P, Tomlinson B, Little J, Creger R, Lazarus H, Cooper B. Concurrent blinatumomab and donor lymphocyte infusions for treatment of relapsed pre-B-cell ALL after allogeneic hematopoietic cell transplant. *Bone Marrow Transplant.* 2016;51(9):1253–5. <https://doi.org/10.1038/bmt.2016.104>
6. Gaballa MR, Banerjee P, Milton DR, Jiang X, Ganesh C, Khazal S, Nandivada V, Islam S, Kaplan M, Daher M, Basar R, Alousi A, Mehta R, Alatrash G, Khouri I, Oran B, Marin D, Popat U, Olson A, Tewari P, Jain N, Jabbour E, Ravandi F, Kantarjian H, Chen K, Champlin R, Shpall E, Rezvani K, Kebriaei P. Blinatumomab maintenance after allogeneic hematopoietic cell transplantation for B-lineage acute lymphoblastic leukemia. *Blood.* 2022;139(12):1908–19. <https://doi.org/10.1182/blood.2021013290>
7. Huang J, Shi B, Yu S, Xue M, Wang L, Jiang J, Hu J, Zhu J, Chen S, Shen L, Cao W, Cao Y, Hu X. Efficacy of blinatumomab as maintenance therapy for B-lineage acute lymphoblastic leukemia/lymphoma following allogeneic hematopoietic cell transplantation. *Blood Cancer J.* 2024;14(1):109. <https://doi.org/10.1038/s41408-024-01092-w>
8. Metheny LL, Sobecks R, Cho C, Fu P, Margevicius S, Wang J, Ciarrone L, Kopp S, Convents RD, Majhail N, Caimi PF, Otegbeye F, Cooper BW, Gallogly M, Malek E, Tomlinson B, Gerds AT, Hamilton B, Giralt S, Perales MA, de Lima M. A multicenter study of posttransplantation low-dose inotuzumab ozogamicin to prevent relapse of acute lymphoblastic leukemia. *Blood Adv.* 2024;8(6):1384–91. <https://doi.org/10.1182/bloodadvances.2023011514>
9. Brissot E, Labopin M, Beckers MM, Socié G, Rambaldi A, Volin L, Finke J, Lenhoff S, Kröger N, Ossenkoppele GJ, Craddock CF, Yakoub-Agha I, Gürman G, Russell NH, Aljurf M, Potter MN, Nagler A, Ottmann O, Cornelissen JJ, Esteve J, Mohty M. Tyrosine kinase inhibitors improve long-term outcome of allogeneic hematopoietic stem cell transplantation for adult patients with Philadelphia chromosome positive acute lymphoblastic leukemia. *Haematologica.* 2015;100(3):392–9. <https://doi.org/10.3324/haematol.2014.116954>
10. Saini N, Marin D, Ledesma C, Delgado R, Rondon G, Popat UR, Bashir Q, Hosing CM, Nieto Y, Alousi AM, Qazilbash MH, Ciurea S, Shpall E, Khouri I, Kantarjian H, Jabbour E, Ravandi F, Champlin RE, Kebriaei P. Impact of TKIs post-allogeneic hematopoietic cell transplantation in Philadelphia chromosome–positive ALL. *Blood.* 2020;136(15):1786–9. <https://doi.org/10.1182/blood.2019004685>
11. Oran B, Champlin R, Thall P, McCarty J, Zhang W, Marin D, Mehta RS, Alousi AM, Alatrash G, Popat UR, Kantarjian H, Bashir Q, Shpall EJ, Konopleva M. Phase II trial of venetoclax (Ven) in combination with azacitidine (AZA) As maintenance therapy for high-risk acute leukemia following allogeneic stem cell transplantation (SCT). *Blood.* 2022;140(Suppl. 1):10561–2. <https://doi.org/10.1182/blood-2022-159312>
12. Hassan MA, Moukalled N, El Cheikh J, Bazarbachi A, Abou Dalle I. Azacitidine in combination with venetoclax maintenance post-allogeneic hematopoietic stem cell transplantation in T cell acute lymphoblastic leukemia. *Clin Hematol Int.* 2023;5(1):52–5. <https://doi.org/10.1007/s44228-022-00019-1>
13. Kungwankiattichai S, Ponvilawan B, Roy C, Tunsing P, Kuchenbauer F, Owattanapanich W. Maintenance with hypomethylating agents after allogeneic stem cell transplantation in acute myeloid leukemia and myelodysplastic syndrome: a systematic review and meta-analysis. *Front Med.* 2022;9:801632. <https://doi.org/10.3389/fmed.2022.801632>
14. Gao L, Zhang Y, Wang S, Kong P, Su Y, Hu J, Jiang M, Bai H, Lang T, Wang J, Liu L, Yang T, Huang X, Liu F, Lou S, Liu Y, Zhang C, Liu H, Gao L, Liu J, Zhu L, Wen Q, Chen T, Wang P, Rao J, Mao M, Wang C, Duan X, Luo L, Peng X, Cassady K, Zhong JF, Zhang X. Effect of rhG-CSF combined with decitabine prophylaxis on relapse of patients with high-risk MRD-negative AML after HSCT: an open-label, multicenter, randomized controlled trial. *J Clin Oncol.* 2020;38(36):4249–59. <https://doi.org/10.1200/jco.19.03277>
15. Kent A, Schwartz M, McMahon C, Amaya M, Smith CA, Tobin J, Marciano K, Rezac R, Bosma G, Pollyea DA, Gutman JA. Venetoclax is safe and tolerable as post-transplant maintenance therapy for AML patients at high risk for relapse. *Bone Marrow Transplant.* 2023;58(8):849–54. <https://doi.org/10.1038/s41409-023-01987-5>

16. Ohga S, Yamauchi T, Yoshimoto G, Kato K, Akashi K. Overcoming high-risk MDS/AML post-allogeneic HSCT: venetoclax and azacitidine as maintenance therapy. *Blood*. 2024;144(Suppl. 1):5973. <https://doi.org/10.1182/blood-2024-202428>
17. Garcia JS, Kim HT, Murdock HM, Ansuinelli M, Brock J, Cutler CS, Gooptu M, Ho VT, Koreth J, Nikiforow S, Romee R, Shapiro R, DeAngelo DJ, Stone RM, Bat-Erdene D, Ryan J, Contreras ME, Fell G, Letai A, Ritz J, Lindsley RC, Soiffer RJ, Antin JH. Prophylactic maintenance with venetoclax/azacitidine after reduced-intensity conditioning allogeneic transplant for high-risk MDS and AML. *Blood Adv*. 2024;8(4):978–90. <https://doi.org/10.1182/bloodadvances.2023012120>
18. Burchert A, Bug G, Fritz LV, Finke J, Stelljes M, Röllig C, Wollmer E, Wäsch R, Bornhäuser M, Berg T, Lang F, Ehninger G, Serve H, Zeiser R, Wagner EM, Kröger N, Wolschke C, Schleuning M, Götze KS, Schmid C, Crysandt M, Eßeling E, Wolf D, Wang Y, Böhm A, Thiede C, Haferlach T, Michel C, Bethge W, Wündisch T, Brandts C, Harnisch S, Wittenberg M, Hoeffkes HG, Rospleszcz S, Burchardt A, Neubauer A, Brugger M, Strauch K, Schade-Brittinger C, Metzelder SK. Sorafenib maintenance after allogeneic hematopoietic stem cell transplantation for acute myeloid leukemia with FLT3-internal tandem duplication mutation (SORMAIN). *J Clin Oncol*. 2020;38(26):2993–3002. <https://doi.org/10.1200/jco.19.03345>
19. Xuan L, Wang Y, Huang F, Fan Z, Xu Y, Sun J, Xu N, Deng L, Li X, Liang X, Luo X, Shi P, Liu H, Wang Z, Jiang L, Yu C, Zhou X, Lin R, Chen Y, Tu S, Huang X, Liu Q. Sorafenib maintenance in patients with FLT3-ITD acute myeloid leukaemia undergoing allogeneic haematopoietic stem-cell transplantation: an open-label, multicentre, randomised phase 3 trial. *Lancet Oncol*. 2020;21(9):1201–12. [https://doi.org/10.1016/s1470-2045\(20\)30455-1](https://doi.org/10.1016/s1470-2045(20)30455-1)
20. Levis MJ, Hamadani M, Logan B, Jones RJ, Singh AK, Litzow M, Wingard JR, Papadopoulos EB, Perl AE, Soiffer RJ, Ustun C, Ueda Oshima M, Uy GL, Waller EK, Vasu S, Solh M, Mishra A, Muffy L, Kim HJ, Mikesch JH, Najima Y, Onozawa M, Thomson K, Nagler A, Wei AH, Marcucci G, Geller NL, Hasabou N, Delgado D, Rosales M, Hill J, Gill SC, Nuthethi R, King D, Wittsack H, Mendizabal A, Devine SM, Horowitz MM, Chen YB; BMT-CTN 1506/MORPHO Study Investigators. Gilteritinib as post-transplant maintenance for AML with internal tandem duplication mutation of FLT3. *J Clin Oncol*. 2024;42(15):1766–75. <https://doi.org/10.1200/jco.23.02474>
21. Miura S, Ueda K, Minakawa K, Nollet KE, Ikeda K. Prospects and potential for chimerism analysis after allogeneic hematopoietic stem cell transplantation. *Cells*. 2024;13(11):993. <https://doi.org/10.3390/cells13110993>
22. Blouin AG, Askar M. Chimerism analysis for clinicians: a review of the literature and worldwide practices. *Bone Marrow Transplant*. 2022;57(3):347–59. <https://doi.org/10.1038/s41409-022-01579-9>
23. Haugaard AK, Madsen HO, Marquart HV, Rosthøj S, Masmus TN, Heilmann C, Müller KG, Ifversen M. Highly sensitive chimerism detection in blood is associated with increased risk of relapse after allogeneic hematopoietic cell transplantation in childhood leukemia. *Pediatr Transplant*. 2019;23(7):13549. <https://doi.org/10.1111/petr.13549>
24. Bader P, Kreyenberg H, von Stackelberg A, Eckert C, Salzmann-Manrique E, Meisel R, Poetschger U, Stachel D, Schrappe M, Alten J, Schrauder A, Schulz A, Lang P, Müller I, Albert MH, Willasch AM, Klingebiel TE, Peters C. Monitoring of minimal residual disease after allogeneic stem-cell transplantation in relapsed childhood acute lymphoblastic leukemia allows for the identification of impending relapse: results of the ALL-BFM-SCT 2003 trial. *J Clin Oncol*. 2015;33(11):1275–84. <https://doi.org/10.1200/jco.2014.58.4631>
25. Wethmar K, Matern S, Eßeling E, Angenendt L, Pfeifer H, Brüggemann M, Stelmach P, Call S, Albring JC, Mikesch JH, Reicherts C, Groth C, Schliemann C, Berdel WE, Lenz G, Stelljes M. Monitoring minimal residual/relapsing disease after allogeneic haematopoietic stem cell transplantation in adult patients with acute lymphoblastic leukaemia. *Bone Marrow Transplant*. 2020;55(7):1410–20. <https://doi.org/10.1038/s41409-020-0801-0>

26. Gang M, Othus M, Walter RB. Significance of measurable residual disease in patients undergoing allogeneic hematopoietic cell transplantation for acute myeloid leukemia. *Cells*. 2025;14(4):290. <https://doi.org/10.3390/cells14040290>
27. Spyridonidis A. How I treat measurable (minimal) residual disease in acute leukemia after allogeneic hematopoietic cell transplantation. *Blood*. 2020;135(19):1639–49. <https://doi.org/10.1182/blood.2019003566>
28. Mo X, Lv M, Huang X. Preventing relapse after haematopoietic stem cell transplantation for acute leukaemia: the role of post-transplantation minimal residual disease (MRD) monitoring and MRD-directed intervention. *Br J Haematol*. 2017;179(2):184–97. <https://doi.org/10.1111/bjh.14778>
29. Pincez T, Santiago R, Bittencourt H, Louis I, Bilodeau M, Rouette A, Jouan L, Landry JR, Couture F, Richer J, Teira P, Duval M, Cellot S. Intensive monitoring of minimal residual disease and chimerism after allogeneic hematopoietic stem cell transplantation for acute leukemia in children. *Bone Marrow Transplant*. 2021;56(12):2981–9. <https://doi.org/10.1038/s41409-021-01408-5>
30. Tavares RDCB, Pelegrina PRD. Prevention and management of relapse of acute leukemia and myelodysplastic syndrome after allogeneic hematopoietic cell transplantation in pediatric patients. *J Bone Marrow Transplant Cell Ther*. 2021;2(4):131. <https://doi.org/10.46765/2675-374X.2021v2n4p131>
31. Llaurador G, Nicoletti E, Prockop SE, Hsu S, Fuller K, Mauguen A, O'Reilly RJ, Boelens JJ, Boulad F. Donor-host lineage-specific chimerism monitoring and analysis in pediatric patients following allogeneic stem cell transplantation: influence of pretransplantation variables and correlation with post-transplantation outcomes. *Transplant Cell Ther*. 2021;27(9):780.e1–e14. <https://doi.org/10.1016/j.jtct.2021.05.020>
32. Horn B, Wahlstrom JT, Melton A, Liou A, Ouachee-Chardin M, Sunkersett G, Willert J, Hwang J, Expose-Spencer J, Cowan MC, Facchino J, Dvorak CC. Early mixed chimerism-based preemptive immunotherapy in children undergoing allogeneic hematopoietic stem cell transplantation for acute leukemia. *Pediatr Blood Cancer*. 2017;64(8):10.1002/pbc.26464. <https://doi.org/10.1002/pbc.26464>
33. Delie A, Verlinden A, Beel K, Deeren D, Mazure D, Baron F, Breems D, De Becker A, Graux C, Lewalle P, Maertens J, Poire X, Schoemans H, Selleslag D, Van Obbergh F, Kerre T. Use of chimerism analysis after allogeneic stem cell transplantation: Belgian guidelines and review of the current literature. *Acta Clin Belg*. 2021;76(6):500–8. <https://doi.org/10.1080/17843286.2020.1754635>
34. Gillissen MA, de Jong G, Levie SE, Yasuda E, Bakker AQ, Evers LM, Pals ST, Huisman C, van Helden PM, Spits H, Hazenberg MD. AML relapse after rituximab treatment for GvHD: crucial role for B cells in GvL responses. *Bone Marrow Transplant*. 2016;51(9):1245–8. <https://doi.org/10.1038/bmt.2016.90>
35. Pagliuca S, Schmid C, Santoro N, Simonetta F, Battipaglia G, Guillaume T, Greco R, Onida F, Sánchez-Ortega I, Yakoub-Agha I, Kuball J, Hazenberg MD, Ruggeri A; Practice Harmonization and Guidelines Committee and the Cellular Therapy and Immunobiology Working Party of the European Society for Blood and Marrow Transplantation (EBMT). Donor lymphocyte infusion after allogeneic haematopoietic cell transplantation for haematological malignancies: basic considerations and best practice recommendations from the EBMT. *Lancet Haematol*. 2024;11(6):e448–58. [https://doi.org/10.1016/s2352-3026\(24\)00098-x](https://doi.org/10.1016/s2352-3026(24)00098-x)
36. Jaiswal SR, Chakrabarti A, Chatterjee S, Bhargava S, Ray K, O'Donnell P, Chakrabarti S. Haploidentical peripheral blood stem cell transplantation with post-transplantation cyclophosphamide in children with advanced acute leukemia with fludarabine-, busulfan-, and melphalan-based conditioning. *Biol Blood Marrow Transplant*. 2016;22(3):499–504. <https://doi.org/10.1016/j.bbmt.2015.11.010>
37. Swaminathan VV, Uppuluri R, Patel S, Sivashankaran M, Ravichandran N, Ramanan KM, Ramakrishnan B, Vaidhyanathan L, Raj R. Safety and efficacy of fresh whole blood donor lymphocyte infusion in children. *Bone Marrow Transplant*. 2019;54(11):1892–7. <https://doi.org/10.1038/s41409-019-0580-7>

38. Vago L, Toffalori C, Ciceri F, Fleischhauer K. Genomic loss of mismatched human leukocyte antigen and leukemia immune escape from haploidentical graft-versus-leukemia. *Semin Oncol.* 2012;39(6):707–15. <https://doi.org/10.1053/j.seminoncol.2012.09.009>
39. Koster EAS, von dem Borne PA, van Balen P, Marijt EWA, Tjon JML, Snijders TJF, van Lammeren D, Veelken H, Falkenburg JHF, Halkes CJM, de Wreede LC. Risk factors for graft-versus-host-disease after donor lymphocyte infusion following T-cell depleted allogeneic stem cell transplantation. *Front Immunol.* 2024;15:1335341. <https://doi.org/10.3389/fimmu.2024.1335341>
40. Geramita E, Hou JZ, Shlomchik WD, Ito S. Maintenance strategies for relapse prevention and treatment. *Hematol Am Soc Hematol Educ Program.* 2024;2024(1):635–43. <https://doi.org/10.1182/hematology.2024000589>
41. Aygüneş U, Karagün BŞ, Şaşmaz I, Antmen AB. The outcome of relapsed childhood acute lymphoblastic leukemia after allogeneic hematopoietic stem-cell transplantations: A single-center experience. *Clin Transplant.* 2024;38(5):15366. <https://doi.org/10.1111/ctr.15366>
42. Horton TM, Whitlock JA, Lu X, O'Brien MM, Borowitz MJ, Devidas M, Raetz EA, Brown PA, Carroll WL, Hunger SP. Bortezomib reinduction chemotherapy in high-risk ALL in first relapse: a report from the Children's Oncology Group. *Br J Haematol.* 2019;186(2):274–85. <https://doi.org/10.1111/bjh.15919>
43. Yanagi M, Mori M, Honda M, Mitani Y, Seki M, Fukuoka K, Oshima K, Arakawa Y, Koh K. Nelarabine-containing salvage therapy and conditioning regimen in transplants for pediatric T-cell acute lymphoblastic leukemia and lymphoma. *Int J Hematol.* 2024;119(3):327–33. <https://doi.org/10.1007/s12185-023-03701-z>
44. Whitlock JA, Malvar J, Dalla-Pozza L, Goldberg JM, Silverman LB, Ziegler DS, Attarbaschi A, Brown PA, Gardner RA, Gaynon PS, Hutchinson R, Huynh VT, Jeha S, Marcus L, Messinger Y, Schultz KR, Cassar J, Locatelli F, Zwaan CM, Wood BL, Sposto R, Gore L. Nelarabine, etoposide, and cyclophosphamide in relapsed pediatric T-acute lymphoblastic leukemia and T-lymphoblastic lymphoma (study T2008-002 NECTAR). *Pediatr Blood Cancer.* 2022;69(11):29901. <https://doi.org/10.1002/pbc.29901>
45. Basile G, Galtier J, Cazaubiel T, Forcade E, Klein E, Bidet A, Botella-Garcia C, Mediavilla C, Clement L, Dumas PY, Pigneux A, Leguay T. Relapsed Philadelphia chromosome-positive B-cell acute lymphoblastic leukaemia responds well to a combination of modified hyper-CVAD, blinatumomab and tyrosine kinase inhibitor. *EJHaem.* 2025;6(1):1064. <https://doi.org/10.1002/jha2.1064>
46. Aubert L, Petit A, Bertrand Y, Ray-Lunven AF, Angoso M, Pluchart C, Millot F, Saultier P, Cheikh N, Pellier I, Plantaz D, Sirvent A, Thouvenin-Doulet S, Valduga J, Plat G, Rialland F, Henry C, Esvan M, Gandemer V. Therapeutic approach and outcome of children with Philadelphia chromosome-positive acute lymphoblastic leukemia at first relapse in the era of tyrosine kinase inhibitors: An SFCE retrospective study. *Pediatr Blood Cancer.* 2022;69(2):e29441. <https://doi.org/10.1002/pbc.29441>
47. Pennesi E, Michels N, Brivio E, van der Velden VHJ, Jiang Y, Thanos A, Ammerlaan AJC, Boer JM, Beverloo HB, Sleight B, Chen Y, Vormoor-Bürger B, Rives S, Bielora B, Rössig C, Petit A, Rizzari C, Engstler G, Starý J, Bautista Sirvent FJ, Chen-Santel C, Bruno B, Bertrand Y, Rialland F, Plat G, Reinhardt D, Vinti L, Von Stackelberg A, Locatelli F, Zwaan CM. Inotuzumab ozogamicin as single agent in pediatric patients with relapsed and refractory acute lymphoblastic leukemia: results from a phase II trial. *Leukemia.* 2022;36(6):1516–24. <https://doi.org/10.1038/s41375-022-01576-3>
48. Rubinstein JD, O'Brien MM. Inotuzumab ozogamicin in B-cell precursor acute lymphoblastic leukemia: efficacy, toxicity, and practical considerations. *Front Immunol.* 2023;14:1237738. <https://doi.org/10.3389/fimmu.2023.1237738>
49. O'Brien MM, Ji L, Shah NN, Rheingold SR, Bhojwani D, Yuan CM, Xu X, Yi JS, Harris AC, Brown PA, Borowitz MJ, Militano O, Kairalla J, Devidas M, Raetz EA, Gore L, Loh ML. Phase II trial of inotuzumab ozogamicin in children and adolescents with relapsed or refractory B-cell acute lymphoblastic leukemia: children's oncology group protocol AALL1621. *J Clin Oncol.* 2022;40(9):956–67. <https://doi.org/10.1200/jco.21.01693>

50. Guo HP, Liu Y, Kang L, Liu C, Qin WW. Efficacy and safety of blinatumomab for the treatment of patients relapsing after allogeneic hematopoietic cell transplantation: a systemic review and meta-analysis. *Hematol Amst Neth*. 2024;29(1):2422151. <https://doi.org/10.1080/16078454.2024.2422151>
51. Bruzzese A, Martino EA, Labanca C, Caridà G, Mendicino F, Lucia E, Olivito V, Puccio N, Neri A, Morabito F, Vigna E, Gentile M. Therapeutic strategies for relapsed or refractory B-cell acute lymphoblastic leukemia in adult patients: optimizing the use of monoclonal antibodies. *Eur J Haematol*. 2025;114(6):938–52. <https://doi.org/10.1111/ejh.14405>
52. Bhatla T, Hogan LE, Teachey DT, Bautista F, Moppett J, Velasco Puyó P, Micalizzi C, Rossig C, Shukla N, Gilad G, Locatelli F, Baruchel A, Zwaan CM, Bezler NS, Rubio-San-Simón A, Taussig DC, Raetz EA, Mao ZJ, Wood BL, Alvarez Arias D, Krevvata M, Nnane I, Bandyopadhyay N, Lopez Solano L, Dennis RM, Carson R, Vora A. Daratumumab in pediatric relapsed/refractory acute lymphoblastic leukemia or lymphoblastic lymphoma: the DELPHINUS study. *Blood*. 2024;144(21):2237–47. <https://doi.org/10.1182/blood.2024024493>
53. Vákrmanová B, Nováková M, Říha P, Žaliová M, Froňková E, Mejstříková E, Starý J, Hrušák O, Šrámková L. CD38: A target in relapsed/refractory acute lymphoblastic leukemia-Limitations in treatment and diagnostics. *Pediatr Blood Cancer*. 2022;69(9):e29779. <https://doi.org/10.1002/pbc.29779>
54. Wilson A, Moussa A, Trinquand A, Malone A, Tewari S, Calvert R, Patrick K, Nicholson E, Smith K, Grandage V, Baird S, George L, Qureshi A, Borg A, Gibson B, Patel P, Bartram J, Samrin L, O'Connor D. Real-world use of venetoclax in the treatment of paediatric and teenage/young adult haematological malignancies. *Br J Haematol*. 2024;205(6):2355–62. <https://doi.org/10.1111/bjh.19791>
55. Pullarkat VA, Lacayo NJ, Jabbour E, Rubnitz JE, Bajel A, Laetsch TW, Leonard J, Colace SI, Khaw SL, Fleming SA, Mattison RJ, Norris R, Opferman JT, Roberts KG, Zhao Y, Qu C, Badawi M, Schmidt M, Tong B, Pesko JC, Sun Y, Ross JA, Vishwamitra D, Rosenwinkel L, Kim SY, Jacobson A, Mullighan CG, Alexander TB, Stock W. Venetoclax and navitoclax in combination with chemotherapy in patients with relapsed or refractory acute lymphoblastic leukemia and lymphoblastic lymphoma. *Cancer Discov*. 2021;11(6):1440–53. <https://doi.org/10.1158/2159-8290.cd-20-1465>
56. Badawi MA, Gopalakrishnan S, Engelhardt B, Palenski TL, Kim SY, Karol SE, Rubnitz JE, Menon R, Salem AH. Proposed scheme for dosing venetoclax in pediatric patients with relapsed/refractory acute myeloid leukemia: analysis of developmental pharmacokinetics and exposure-response relationships. *Blood*. 2020;136(Suppl. 1):11–2. <https://doi.org/10.1182/blood-2020-139593>
57. Varadarajan I, Pierce E, Scheuing L, Morris A, El Chaer F, Keng M. Post-hematopoietic cell transplantation relapsed acute lymphoblastic leukemia: current challenges and future directions. *OncoTargets Ther*. 2023;16:1–16. <https://doi.org/10.2147/ott.s274551>
58. Wang SS, Abbott RC, Gilsenan M, Duke T, Khaw SL. Chimeric antigen receptor T cell therapy in childhood leukaemia. *Arch Dis Child*. 2025;110(7):503–9. <https://doi.org/10.1136/archdischild-2024-328263>
59. Jacoby E, Ghorashian S, Vormoor B, De Moerloose B, Bodmer N, Molostova O, Yanir AD, Buechner J, Elhasid R, Bielora B, Rogosic S, Dourthe ME, Maschan M, Rossig C, Toren A, von Stackelberg A, Locatelli F, Bader P, Zimmermann M, Bourquin JP, Baruchel A. CD19 CAR T-cells for pediatric relapsed acute lymphoblastic leukemia with active CNS involvement: a retrospective international study. *Leukemia*. 2022;36(6):1525–32. <https://doi.org/10.1038/s41375-022-01546-9>
60. Schultz LM, Baggott C, Prabhu S, Pacenta HL, Phillips CL, Rossoff J, Stefanski HE, Talano JA, Moskop A, Margossian SP, Verneris MR, Myers GD, Karras NA, Brown PA, Qayed M, Hermiston M, Satwani P, Krupski C, Keating AK, Wilcox R, Rabik CA, Fabrizio VA, Rouce RH, Chinnabhandar V, Kunicki M, Barsan VV, Goksenin AY, Li Y, Mavroukakis S, Egeler E, Curran KJ, Mackall CL, Laetsch TW. Disease burden affects outcomes in pediatric and young adult B-cell lymphoblastic leukemia after commercial tisagenlecleucel: a pediatric real-world chimeric antigen receptor consortium report. *J Clin Oncol*. 2022;40(9):945–55. <https://doi.org/10.1200/jco.20.03585>

61. Mahadeo KM, Khazal SJ, Abdel-Azim H, Fitzgerald JC, Taraseviciute A, Bollard CM, Tewari P, Duncan C, Traube C, McCall D, Steiner ME, Cheifetz IM, Lehmann LE, Mejia R, Slopis JM, Bajwa R, Kebriaei P, Martin PL, Moffet J, McArthur J, Petropoulos D, O'Hanlon Curry J, Featherston S, Foglesong J, Shoberu B, Gulbis A, Mireles ME, Hafemeister L, Nguyen C, Kapoor N, Rezvani K, Neelapu SS, Shpall EJ; Pediatric Acute Lung Injury and Sepsis Investigators (PALISI) Network. Management guidelines for paediatric patients receiving chimeric antigen receptor T cell therapy. *Nat Rev Clin Oncol*. 2019;16(1):45–63. <https://doi.org/10.1038/s41571-018-0075-2>
62. Ortí G, Peczynski C, Boreland W, O'Reilly M, von Bonin M, Balduzzi A, Besley C, Kalwak K, Ryhänen S, Güngör T, Wynn RF, Bader P, Mielke S, Blaise D, Amrolia P, Yakoub-Agha I, Calkoen F, Schubert ML, Potter V, Pichler H, Kröger N, Kwon M, Sengeloev H, Torrent A, Chalandon Y, van Gorkom G, Koenecke C, Graham C, Schoemans H, Moiseev I, Penack O, Peric Z. Graft-versus-host disease after anti-CD19 chimeric antigen receptor T-cell therapy following allogeneic hematopoietic cell transplantation: a transplant complications and paediatric diseases working parties joint EBMT study. *Leukemia*. 2025;39(2):431–7. <https://doi.org/10.1038/s41375-024-02467-5>
63. de Melo Rodrigues AL, Bonfim C, Seber A, Colturato VAR, Zecchin VG, Nichele S, Daudt LE, Fernandes JF, Vieira AK, Darrigo Junior LG, Gomes AA, Arcuri L, Lenzi L, Picharski GL, Ribeiro RC, de Figueiredo BC. Allogeneic hematopoietic stem cell transplantation for children and adolescents with acute myeloid leukemia in Brazil: a multicentric retrospective study. *Cell Transplant*. 2020;29:963689720949175. <https://doi.org/10.1177/0963689720949175>
64. Egan G, Tasian SK. Relapsed pediatric acute myeloid leukaemia: state-of-the-art in 2023. *Haematologica*. 2023;108(9):2275–88. <https://doi.org/10.3324/haematol.2022.281106>
65. Rasche M, Zimmermann M, Steidel E, Alonzo T, Aplenc R, Bourquin JP, Boztug H, Cooper T, Gamis AS, Gerbing RB, Janotova I, Klusmann JH, Lehrnbecher T, Mühlegger N, Neuhoﬀ NV, Niktoreh N, Sramkova L, Stary J, Waack K, Walter C, Creutzig U, Dworzak M, Kaspers G, Kolb EA, Reinhardt D. Survival following relapse in children with acute myeloid leukemia: a report from AML-BFM and COG. *Cancers*. 2021;13(10):2336. <https://doi.org/10.3390/cancers13102336>
66. Rasche M, Steidel E, Zimmermann M, Bourquin JP, Boztug H, Janotova I, Kolb EA, Lehrnbecher T, von Neuhoﬀ N, Niktoreh N, Mühlegger N, Sramkova L, Stary J, Walter C, Creutzig U, Dworzak M, Reinhardt D. Second relapse of pediatric patients with acute myeloid leukemia: a report on current treatment strategies and outcome of the AML-BFM study group. *Cancers*. 2021;13(4):789. <https://doi.org/10.3390/cancers13040789>
67. DiNardo CD, Lachowicz CA, Takahashi K, Loghavi S, Xiao L, Kadia T, Daver N, Adeoti M, Short NJ, Sasaki K, Wang S, Borthakur G, Issa G, Maiti A, Alvarado Y, Pemmaraju N, Montalban Bravo G, Masarova L, Yilmaz M, Jain N, Andreeff M, Jabbour E, Garcia-Manero G, Kornblau S, Ravandi F, Konopleva MY, Kantarjian HM. Venetoclax combined with FLAG-IDA induction and consolidation in newly diagnosed and relapsed or refractory acute myeloid leukemia. *J Clin Oncol*. 2021;39(25):2768–78. <https://doi.org/10.1200/jco.20.03736>
68. Masetti R, Baccelli F, Leardini D, Gottardi F, Vendemini F, Di Gangi A, Becilli M, Lodi M, Tumino M, Vinci L, Erlacher M, Strahm B, Niemeyer CM, Locatelli F. Venetoclax-based therapies in pediatric advanced MDS and relapsed/refractory AML: a multicenter retrospective analysis. *Blood Adv*. 2023;7(16):4366–70. <https://doi.org/10.1182/bloodadvances.2023010113>
69. Pommert L, Tarlock K. The evolution of targeted therapy in pediatric AML: gemtuzumab ozogamicin, FLT3/IDH/BCL2 inhibitors, and other therapies. *Hematol Am Soc Hematol Educ Program*. 2022;2022(1):603–10. <https://doi.org/10.1182/hematology.2022000358>

70. Karol SE, Gueguen G. Pediatric acute myeloid leukemia - novel approaches. *Curr Opin Hematol*. 2024;31(2):47–52. <https://doi.org/10.1097/MOH.0000000000000795>
71. Lambie AJ, Tasian SK. Opportunities for immunotherapy in childhood acute myeloid leukemia. *Blood Adv*. 2019;3(22):3750–8. <https://doi.org/10.1182/bloodadvances.2019000357>
72. Caruso S, De Angelis B, Del Bufalo F, Ciccone R, Donsante S, Volpe G, Manni S, Guercio M, Pezzella M, Iaffaldano L, Silvestris DA, Sinibaldi M, Di Cecca S, Pitisci A, Velardi E, Merli P, Algeri M, Lodi M, Paganelli V, Serafini M, Riminucci M, Locatelli F, Quintarelli C. Safe and effective off-the-shelf immunotherapy based on CAR-CD123-NK cells for the treatment of acute myeloid leukaemia. *J Hematol Oncol*. 2022;15(1):163. <https://doi.org/10.1186/s13045-022-01376-3>
73. Bednarski JJ, Zimmerman C, Berrien-Elliott MM, Foltz JA, Becker-Hapak M, Neal CC, Foster M, Schappe T, McClain E, Pence PP, Desai S, Kersting-Schadek S, Wong P, Russler-Germain DA, Fisk B, Lie WR, Eisele J, Hyde S, Bhatt ST, Griffith OL, Griffith M, Petti AA, Cashen AF, Fehniger TA. Donor memory-like NK cells persist and induce remissions in pediatric patients with relapsed AML after transplant. *Blood*. 2022;139(11):1670–83. <https://doi.org/10.1182/blood.2021013972>
74. Knight TE, Edwards H, Meshinchi S, Taub JW, Ge Y. “FLipping” the story: FLT3-mutated acute myeloid leukemia and the evolving role of FLT3 inhibitors. *Cancers*. 2022;14(14):3398. <https://doi.org/10.3390/cancers14143398>
75. Pollard JA, Alonzo TA, Gerbing R, Brown P, Fox E, Choi J, Fisher B, Hirsch B, Kahwash S, Getz K, Levine J, Brodersen LE, Loken MR, Raimondi S, Tarlock K, Wood A, Sung L, Kolb EA, Gamis A, Meshinchi S, Aplenc R. Sorafenib in combination with standard chemotherapy for children with high allelic ratio FLT3/ITD+ acute myeloid leukemia: a report from the Children’s Oncology Group Protocol AAML1031. *J Clin Oncol*. 2022;40(18):2023–35. <https://doi.org/10.1200/jco.21.01612>
76. Sweeney C, Vyas P. The graft-versus-leukemia effect in AML. *Front Oncol*. 2019;9:1217. <https://doi.org/10.3389/fonc.2019.01217>
77. Shah NA. Donor lymphocyte infusion in acute myeloid leukemia. *Best Pract Res Clin Haematol*. 2023;36(3):101484. <https://doi.org/10.1016/j.beha.2023.101484>
78. Yalniz FF, Patel KP, Bashir Q, Marin D, Ahmed S, Alousi AM, Chen J, Ciurea SO, Rezvani K, Popat UR, Shpall EJ, Champlin RE, Oran B. Significance of minimal residual disease monitoring by real-time quantitative polymerase chain reaction in core binding factor acute myeloid leukemia for transplantation outcomes. *Cancer*. 2020;126(10):2183–92. <https://doi.org/10.1002/cncr.32769>
79. Graff Z, Wachter F, Eapen M, Lehmann L, Cooper T. Navigating treatment options and communication in relapsed pediatric AML. *Am Soc Clin Oncol Educ Book*. 2024;44(3):e438690. [https://doi.org/10.1200/edbk\\_438690](https://doi.org/10.1200/edbk_438690)
80. Willasch AM, Salzmann-Manrique E, Krenn T, Duerken M, Faber J, Opper J, Kreyenberg H, Bager R, Huenecke S, Cappel C, Bremm M, Pfirrmann V, Merker M, Ullrich E, Bakhtiar S, Rettinger E, Jarisch A, Soerensen J, Klingebiel TE, Bader P. Treatment of relapse after allogeneic stem cell transplantation in children and adolescents with ALL: the Frankfurt experience. *Bone Marrow Transplant*. 2017;52(2):201–8. <https://doi.org/10.1038/bmt.2016.224>
81. Sakaguchi H, Miyamura T, Tomizawa D, Taga T, Ishida H, Okamoto Y, Koh K, Yokosuka T, Yoshida N, Sato M, Noguchi M, Okada K, Hori T, Takeuchi M, Kosaka Y, Inoue M, Hashii Y, Atsuta Y. Effect of extramedullary disease on allogeneic hematopoietic cell transplantation for pediatric acute myeloid leukemia: a nationwide retrospective study. *Bone Marrow Transplant*. 2021;56(8):1859–65. <https://doi.org/10.1038/s41409-021-01250-9>

82. Shem-Tov N, Saraceni F, Danylesko I, Shouval R, Yerushalmi R, Nagler A, Shimoni A. Isolated extramedullary relapse of acute leukemia after allogeneic stem cell transplantation: different kinetics and better prognosis than systemic relapse. *Biol Blood Marrow Transplant.* 2017;23(7):1087–94. <https://doi.org/10.1016/j.bbmt.2017.03.023>
83. Harris AC, Kitko CL, Couriel DR, Braun TM, Choi SW, Magenau J, Mineishi S, Pawarode A, Yanik G, Levine JE. Extramedullary relapse of acute myeloid leukemia following allogeneic hematopoietic stem cell transplantation: incidence, risk factors and outcomes. *Haematologica.* 2013;98(2):179–84. <https://doi.org/10.3324/haematol.2012.073189>
84. Frietsch JJ, Hunstig F, Wittke C, Junghanss C, Franiel T, Scholl S, Hochhaus A, Hilgendorf I. Extra-medullary recurrence of myeloid leukemia as myeloid sarcoma after allogeneic stem cell transplantation: impact of conditioning intensity. *Bone Marrow Transplant.* 2021;56(1):101–9. <https://doi.org/10.1038/s41409-020-0984-4>
85. Huang Q, Reddi D, Chu P, Snyder DS, Weisenburger DD. Clinical and pathologic analysis of extramedullary tumors after hematopoietic stem cell transplantation. *Hum Pathol.* 2014;45(12):2404–10. <https://doi.org/10.1016/j.humpath.2014.07.022>
86. Goyal SD, Zhang MJ, Wang HL, Akpek G, Copelan EA, Freytes C, Gale RP, Hamadani M, Inamoto Y, Kamble RT, Lazarus HM, Marks DI, Nishihori T, Olsson RF, Reshef R, Ritchie DS, Saber W, Savani BN, Seber A, Shea TC, Tallman MS, Wirk B, Bunjes DW, Devine SM, de Lima M, Weisdorf DJ, Uy GL. Allogeneic hematopoietic cell transplant for AML: no impact of pre-transplant extramedullary disease on outcome. *Bone Marrow Transplant.* 2015;50(8):1057–62. <https://doi.org/10.1038/bmt.2015.82>
87. Kuhlen M, Willasch AM, Dalle JH, Wachowiak J, Yaniv I, Ifversen M, Sedlacek P, Guengoer T, Lang P, Bader P, Suflarska S, Balduzzi A, Strahm B, von Luetlichau I, Hoell JI, Borkhardt A, Klingebiel T, Schrappe M, von Stackelberg A, Glogova E, Poetschger U, Meisel R, Peters C. Outcome of relapse after allogeneic HSCT in children with ALL enrolled in the ALL-SCT 2003/2007 trial. *Br J Haematol.* 2018;180(1):82–9. <https://doi.org/10.1111/bjh.14965>
88. Pastore F, Levine RL. Epigenetic regulators and their impact on therapy in acute myeloid leukemia. *Haematologica.* 2016;101(3):269–78. <https://doi.org/10.3324/haematol.2015.140822>
89. Hazar V, Karasu GT, Uygun V, Özbek N, Karakükçü M, Öztürk G, Daloğlu H, Kılıç SÇ, Aksu T, Ünal E, Koçak Ü, Yeşilipek A, Akçay A, Gürsel O, Küpesiz A, Okur FV, İleri T, Kansoy S, Bayram İ, Karagün BŞ, Gökçe M, Kaya Z, Ok Bozkaya İ, Patıroğlu T, Aksoylar S. Role of a second transplantation for children with acute leukemia following posttransplantation relapse: a study by the Turkish Bone Marrow Transplantation Study Group. *Leuk Lymphoma.* 2020;61(6):1465–74. <https://doi.org/10.1080/10428194.2020.1716220>
90. Hazar V, Tezcan Karasu G, Öztürk G, Küpesiz A, Aksoylar S, Özbek N, Uygun V, İleri T, Okur FV, Koçak Ü, Kılıç SÇ, Akçay A, Güler E, Kansoy S, Karakükçü M, Bayram İ, Aksu T, Yeşilipek A, Karagün BŞ, Yılmaz Ş, Ertem M, Uçkan D, Fışgın T, Gürsel O, Yaman Y, Bozkurt C, Gökçe M; Turkish Pediatric Bone Marrow Transplantation Study Group. Prognostic factors for survival in children who relapsed after allogeneic hematopoietic stem cell transplantation for acute leukemia. *Pediatr Transplant.* 2021;25(5):e13942. <https://doi.org/10.1111/petr.13942>
91. Yaniv I, Krauss AC, Beohou E, Dalissier A, Corbacioglu S, Zecca M, et al. Second hematopoietic stem cell transplantation for post-transplantation relapsed acute leukemia in children: a retrospective EBMT-PDWP study. *Biol Blood Marrow Transplant.* 2018;24(8):1629–42. <https://doi.org/10.1016/j.bbmt.2018.03.002>