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 CAR T-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 ≥ 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[1]. 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[2].

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[3].

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)[4–7]	Highest risk, pre- and/or post-HCT CD19+ MRD	15 mcg/m²/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[8]	Highest risk, and/or post-HCT CD19 neg CD22+ MRD; disease refractory to blinatumomab	0.3–0.6 mg/m²	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)[9,10]	All Ph+ ALL, if BCR-ABL+ before or after HCT. Individualize the decision between prophylactic or preemptive use. Prophylactic: for patients with +MRD pre-HCT or ≥ CR2 or BCR-ABL kinase mutation. Preemptive: for patients with GVHD	Imatinib: 260 mg/m² increased up to 300 mg/m² 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. If preemptive approach: 2 years from first MRD negative or chimerism conversion
T-ALL	Azacitidine + venetoclax[11,12]	Highest-risk T-ALL patients, previously refractory or MRD+ prior to HCT	AZA: 32 mg/m² for five days in 28-day cycles	Myelosuppression, mild GI symptoms	AZA: six cycles
			Venetoclax: 100 mg/m² for 7–14 days starting with AZA, adjusted according to cytopenias		One year of venetoclax
AML	Azacitidine[13]	High-risk AML without targetable mutations	32 mg/m² for five days in 28-day cycles	Myelosuppression	6–12 cycles (every 28 days)
	Decitabine + G-CSF[14]	Alternative to AZA in patients with low blood counts	Decitabine: 5 mg/m² D1-D5 every between six and eight weeks; G-CSF: 100 mg/m² D0-D5	Myelosuppression	Six cycles (every six to eight weeks)
	Venetoclax[15–17]	Alternative to AZA/decitabine	100 mg/m² for 7–14 days, monthly cycles adjusted if myelosuppression	Myelosuppression Mild GI symptoms	One year
FLT3 ITD+ AML	Sorafenib[18,19]	All FLT3+ AML	100–200 mg/m²/day	Myelosuppression, cardiovascular, diarrhea	One year
	Gilteritinib[20]	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[19–23]. 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[24]. 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[25]. For acute lymphoblastic leukemia (ALL), combined qPCR and donor chimerism monitoring optimizes relapse prediction[25]. 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[26–29].

CHIMERISM AND MANAGEMENT OF MIXED CHIMERISM

Chimerism after allogenic HCT is classified as complete donor (CC), mixed (MC), split, or absent as defined by the Brazilian Society of Bone Marrow Transplantation consensus[30]. MC can be stable, increasing, or decreasing[31]. 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[21].

Monitoring schedule

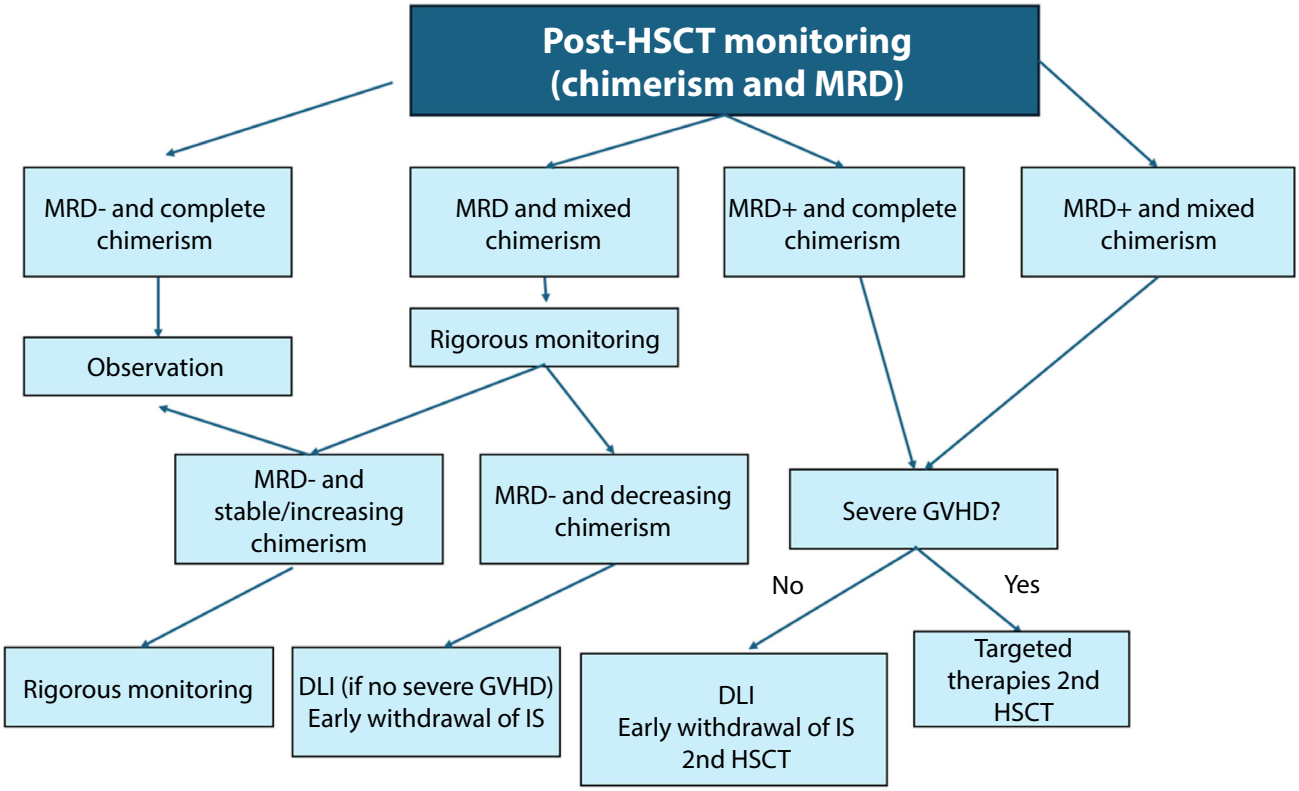
Perform chimerism collection (which can alternate between marrow/peripheral blood sources for each collection) according to clinical decision at the time, every two weeks until day 90, monthly in the first year and then annually until two years post-transplant at least. In some cases, collection may 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[24]. 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[29]. Interventions include rapid immunosuppression tapering with or without escalated donor lymphocyte infusions (DLIs). The DLI protocol recommends initial doses of 1×10^5–10^6 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[32,33].

DONOR LYMPHOCYTE INFUSION

DLI has been used for over 30 years to enhance the graft-*versus*-leukemia (GVL) effect following allogenic 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[21]. 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+, ≥ CR2 or second transplant;
- Preemptive: increasing mixed chimerism, MRD positivity post-transplant (after immunosuppression withdrawal for ≥ 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[3,34];



Source: based on Miura et al.[21]. 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 allogenic hematopoietic cell transplantation for leukemia.

Table 2. Donor lymphocyte infusion strategies, according to indications, donor type, and time after hematopoietic cell transplantation[34–37].

Strategy	Indications	First dose DLI (CD3/kg of weight)
Prophylactic DLI	Standard: - high risk at diagnosis; - advanced or refractory disease at HCT (T-depletion ex-vivo) Optional: - RIC or NMA; - absence of target drugs	3 m: MSD/MUD / HAPLO: 1×10^5; 6 m: MUD/MSD: 1×10^6, HAPLO: 5×10^5 one to three doses with 0.5-log increase for both timepoints
Pre-emptive DLI	Standard: - MC or +MRD; - Molecular or cytogenetic relapse Optional: - Infections/ previous rituximab use	3 m: MSD $1–5\times10^5$; MUD and HAPLO: 1×10^5; one to four doses. 6 m: MUD/MSD: $1–3\times10^6$, MUD: 1×10^6; HAPLO: 5×10^5; one to four doses
Therapeutic DLI	Standard: hematological and extramedullary relapses Optional: post-transplant lymphoproliferative disorders	After systemic therapy: MSD and MUD 1×10^7; HAPLO: 1×10^6; one to four doses (every four to six weeks), with increase of up to 1 log (maximum total dose 1×10^8)
G-DLI + CSA	Advanced or refractory disease at HCT. Contraindicated with any sign of GVHD	D+21 (10^6); D+35 and D+60 (5×10^6); 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: 1×10^5; HAPLO: 1×10^4; one to three doses escalating 0.5-log in each

Source: adapted from Pagliuca et al.[35]. 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[35]. DLI is ineffective for relapses with HLA expression loss (30% of acute myeloid leukemia relapses)[36–38];

• 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 < 1,000×10^6/L (HR = 2.05), and viral infections near DLI administration (HR = 3.66)[39].

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[40].

Salvage chemotherapy options

• IDA-FLAG: achieves complete remission in a significant proportion with modest survival[30,41];

• Bortezomib-based regimens limited efficacy; a Japanese phase-2 study showed no significant improvement. Still investigational for post-HCT relapse[30,42];

• Nelarabine-based regimens are effective in relapsed/refractory T-cell ALL, with manageable toxicity[43,44].

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[30,45,46];

• Inotuzumab ozogamicin (InO), CD22-directed antibody-drug conjugate; complete remission rates of 58.3%; dose: 1.8 mg/m^2/cycle (fractionated), reduced to 1.5 mg/m^2/cycle post-remission; risk of sinusoidal obstruction syndrome[47–49];

• Blinatumomab, bispecific T-cell engager (CD19/CD3); complete remission in 48%, one-year survival of 40%; administered as four-week continuous infusion [50,51];

• Daratumumab, anti-CD38 monoclonal antibody; promising for T-ALL (41.7% complete remission); dosing: 16 mg/kg IV weekly (cycles 1–2), then biweekly [52,53];

• Venetoclax, CL-2 inhibitor; 61% complete remission in retrospective studies; weight-based dosing: 10–600 mg daily in 28-day cycles[54–56];

• Emerging therapies: immune checkpoint inhibitors (pembrolizumab, nivolumab) and menin inhibitors for KMT2A-rearranged ALL show promise but require further validation[57].

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

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

ACUTE MYELOID LEUKEMIA RELAPSE TREATMENT

Relapse of acute myeloid leukemia (AML) following allogenic 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[63–66]. 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[4,64,67,68]	FLAG/IDA-FLAG protocols; venetoclax + HMA (decitabine, azacytidine)	Emerging venetoclax combinations: promising efficacy and lower toxicity profile
Immunotherapy[69–73]	Gemtuzumab ozogamicin (anti-CD33); CAR-T cell therapy; cytokine-induced memory-like NK cells	CAR-T approaches: still investigational Various targets: good preliminary results
Targeted therapy[69,70,74,75]	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[76,77]	Reduction of immunosuppression, donor lymphocyte infusion	Balance between GVL and GVHD risk; the timing of intervention is critical
Second transplantation[65,66,78,79]	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 allogenic HCT[80–82]. Children are three times more likely than adults to develop extramedullary relapse post-transplant[83].

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)[82,84].

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[82]. 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[85]

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[80,86];
- DLI, though less effective in extramedullary relapse[80,87];
- Second allogenic HCT: for patients with good performance status and salvage response[86];
- Local radiotherapy, which does not prevent future extramedullary relapses;
- Hypomethylating agents potentially enhance GVL effect[88].

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[89]. Identifying prognostic factors is essential for patient selection and outcome optimization[90].

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)[91].

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. C**onception 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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