Review

Allogeneic Hematopoietic Stem Cell Transplantation in Infant Leukemia: Vague Prospects? (Series Cases and Brief Review)

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Posted Date: 26 August 2025

doi: 10.20944/preprints202508.1869.v1

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Allogeneic Hematopoietic Stem Cell Transplantation in Infant Leukemia: Vague Prospects? (Series Cases and Brief Review)

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Highlights

- Acute leukemia in children under one year of age is a very rare disease with an unfavorable prognosis and complex treatment.
- The study analyzed 52 publications and the experience of our own center (11 patients who underwent allogeneic stem cell transplantation in 2021–2023). Stem cell transplantation in infants with leukemia is possible.
- Stem cell transplantation in infants with leukemia is possible, but requires an individual approach.

Abstract

Background/Objectives: Acute leukemias (AL) in children under 1 year old are combined under the term "infant leukemia" and are a very rare malignancies, accounting for up to 5% of all childhood AL cases. The predominance of unfavorable clinical and laboratory characteristics leads to unsatisfactory treatment results, even with the use of modern treatment protocols. Patients /Methods: A comprehensive search through MEDLINE, PubMed, Scopus, and ScienceDirect using the infant leukemia-related keywords was performed and included a final set of 52 academic articles. Our own experience included 11 patients with infant leukemia underwent allo-HSCT (allogeneic hematopoietic stem cell transplantation) in NN Blokhin National Medical Research Center of Oncology in 2021-2023. Types of leukemia included acute myeloid leukemia, lymphoblastic leukemia, and mixed-phenotype acute leukemia. The most frequent cytogenetic aberration was KMT2A. All patients were in first complete remission. Donors: haploidentical – 5 (45.4%), matched related donor – 1 (9.2%), matched unrelated donor – 5 (45.4%). Graft manipulations: post-transplant cyclophosphamide was given to 2 patients with haplo-HSCT, and TCRαβ/CD19 depletion was performed in 3 patients. The type of immunosuppressive therapy (IST) varied based on the donor. Conditioning regimens were myeloablative. Results: Median follow-up was 23.5 months. Acute GVHD grade I–II developed in 2 patients (18%), and grade III–IV in 3 patients (27%). The current survival rate is 64% (n=7). The relapse rate after allo-HSCT was 9%. The most common cause of treatment failure was infectious complications in the early post-transplant period. Conclusions: Our center's experience demonstrated acceptable transplant-related mortality and satisfactory relapse rates after allo-HSCT in patients with infant leukemia. The treatment of acute leukemia in infants is challenging and optimal protocols are being developed around the world specifically for these patients. Taking into account the characteristics of this age group, the

 doi:10.20944/preprints202508.1869.v1

choice of chemotherapy drug doses should be carefully considered and the indications for allo-HSCT should be balanced.

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1. Introduction

Infant acute leukemia (IL) is a subset of malignancies affecting children under 1 year of age at diagnosis. The average incidence of IL in the United States is 41 cases per 1 million newborns per year [1]. World statistics showed a significant increase in the incidence of acute lymphoblastic leukemia (ALL) and acute myeloid leukemia (AML) in infants between 1975 and 1989 of approximately 2.5% per year [2]. The incidence of ALL in infants is much lower than in children aged 1 to 14 years and is about the same as in adolescents. In contrast, the incidence of AML in infants is about twice as high as in older children and adolescents. The ratio of ALL/AML is about 60% and 40%, respectively [1–3]. This group of patients is considered to have the worst survival rates and prognostic factors. It accounts for 1% of all pediatric ALLs. Most cases are B-lineage ALL, while T-lineage and mixed phenotype (MPAL) represent a small percentage. The age of the patient is important for the prognosis of survival in pediatric leukemia. In contrast to acute myeloid leukemia (AML), ALL is characterized by poorer outcomes in infants compared to older children with similar cytogenetic characteristics. In addition, pediatric leukemias are characterized by aggressive symptoms, high-risk cytogenetic features associated with resistance to chemotherapy, high relapse rates, and increased toxicity and long-term effects of therapy [2,3]. In particular, *KMT2A*-rearranged ALL types are characterized by hyperleukocytosis, a relatively high incidence of central nervous system (CNS) involvement, an aggressive course, and early relapses leading to a poor prognosis. Researchers have observed that different types of rearrangements in the *KMT2A* gene, very high leukocyte count, age less than 6 months, and poor response to prednisone prophase are independent poor prognostic factors [4,5]. Cytogenetic analysis plays a key role in diagnosing and assessing risk in infant leukemia. *KMT2A* rearrangements in children with AML - including monocytic (FAB M5) myelomonocytic (FAB M4) and megakaryoblastic (FAB M7) subtypes can affect the prognosis in different ways, depending on the specific partner gene. Testing for megakaryocytic markers in all cases of infant leukemia is important because diagnosing megakaryoblastic leukemia can be difficult. Additionally, transient abnormal myelopoiesis, which resembles acute megakaryoblastic leukemia in both morphology and immunophenotype, frequently affects infants with Down syndrome and is characterized by a unique somatic mutation in *GATA1*[6]. Although the pathogenesis of IL in children younger than 1 year of age unclear, there is no doubt that the onset usually occurs in utero, is strongly associated with the presence of predisposing genes as well as leukemogenic exogenous exposure (chemicals, ionizing rays) [1,4,7]. During the early stages of pregnancy, the growing fetus is more sensitive to the effects of potential DNA damage. The etiology of acute leukemia in infants with *KTM2A*-r may be related to transplacental exposure to DNA topoisomerase inhibitors. Topoisomerase inhibitors include chemotherapeutics benzene metabolites such as benzoquinones, isoflavones, flavonoids, lignans, podophyllin resins, quinolone antibiotics and some pesticides [1,7].

Recent international studies (e.g., Interfant Study Group, COG protocols) have shown that the three-year overall survival rate for infants with acute lymphoblastic leukemia following allogeneic HSCT is approximately 40–60%. However, transplantation is discussed more frequently in patients with adverse cytogenetic variants, particularly those with *KMT2A*/*AF1* genetic alterations and a poor response to initial treatment.

In some cases, current chemotherapeutic protocols show similar results to those of transplantation, even in patients with an aggressive disease course, especially in infants without extremely high-risk factors. International practices shows that the decision for allo-HSCT is made on a case-by-case basis in a multidisciplinary consultation involving transplant specialists, oncologists,

 doi:10.20944/preprints202508.1869.v1

and pediatricians, taking into account the response to treatment by minimal residual disease (MRD) and cytogenetic characteristics of IL.

2. Materials and Methods

A comprehensive search was performed through MEDLINE, PubMed, Scopus, and ScienceDirect using the following keywords: “hematopoietic stem cell transplantation”, “infant leukemia”, “treatment”, “diagnostic”, “clinical trial” in the title and abstract, and in the sections of review, systematic review, meta-analysis, clinical trial and randomized clinical trials, and we opted for articles published within the last 10 years in the English language. Of the articles that emerged, the most recent ones were selected, and especially the ones that focused on diagnostic approaches in patients with IL published papers over the last decade. The final set included 52 academic articles related to the topics of interest.

In NN Blokhin National Medical Research Center of Oncology (Moscow) in 2021-2023 eleven patients with infant leukemia underwent allo-HSCT. Eleven patients diagnosed with IL, median age was 5.7 months (0 to 11 months) were included in the study . There were 6 (54.5 %) patients with AML, 3 (27.2 %) patients with ALL and 1 (18.1 %) infant with mixed-phenotype acute leukemia. KMT2A gene rearrangement was observed in 6 (54.5%) patients. Median time from diagnosis to allo-HSCT was 6 months (from 3 to 11 months). Patients were treated according to the protocols: AML-BFM 2004, AML-MRD 2018, ALL-IC BFM 2009. Gender distribution was as follows: 5 girls and 6 boys. As a donor was equally distributed haploidentical - 5 (45.4%) and matched unrelated donor - 5 (45.4%) one patient had matched related donor - 1 (9.2%). The transplantation sources used were bone marrow - 2 pts, peripheral blood stem cells - 9 pts. The median cell dose infused was 3.0 × 108 total nucleated cells per kilogram. Posttransplant cyclophosphamide was administered to 2 patients with haplo-HSCT, and TCR$\alpha\beta$/CD19 depletion was performed in 3 patients. Conditioning regimens were myeloablative with reduced toxicity and included Fludarabine 120 -150mg/m2, Treosulfan 36 g/m2 or Busulfan 12 mg/kg, Thiotepa 5-10 mg/kg or Melfalan 100-120 mg/m2. Drug doses were calculated per square meter regardless of the child’s weight. Patients with TCR$\alpha\beta$/CD19 did not receive standard immunosuppressive therapy (IST) for prevention of graft-versus-host reactions (they received abatacept/tocilizumab/abatacept alone on day-1); the others received combined IST with calcineurin inhibitors and abatacept (Table 2).

3. Results

3.1. Diagnosis

3.1.1. Genetics

The most common form of IL is characterized by cytogenetically balanced chromosomal translocations that include a mixed lineage leukemia gene (KMT2A gene previously named as MLL) on chromosome 11q23 and was described for the first time in 1991–1992 [5,7]. Fetal and neonatal hematopoietic progenitor cells may be particularly susceptible to the effects of KMT2A fusion proteins [1]. Women and men have similar frequencies of KMT2A-r. KMT2A rearrangements (KMT2A-r) occur in up to 5% of ALL cases in children of all ages with a predominance of 70 to 80% in childhood ALL. KMT2A-r in AML is most common in the group of IL - 50%. Rearrangement of the KMT2A gene results in fusion of the N-terminus of the KMT2A with the C-terminus of the KMT2A gene [1,13]. To date more than 80 different partner genes have been identified KMT2A. In infant ALL, 4 partner genes account for 93% of cases: AF4 (49%), ENL (22%), AF9 (17%) and AF10 (5%) [8]. KMT2A-r in infants with ALL has a well-defined gene expression profile. One of the features is the overexpression of FLT3. FLT3 signaling in these either by activating mutations or, more commonly, by autocrine activation by co-expressed autocrine activation by co-expression of ligand FLT3[9]. FLT3 overexpression has been shown to have a prognostic unfavorable, especially in children under 1 year of age with KMT2A-r ALL [10]. The specific expression of chondroitin sulfate proteoglycan-4, also

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known as neutron glial antigen-2 (NG2), is also characteristic of KMT2A-r ALL [9,10,15]. It is a transmembrane proteoglycan that has very low expression in normal hematopoietic cells. NG2 expression is common with KMT2A-r ALL (about 90% of cases). NG2 has been the subject of much recent investigation and has become a novel therapeutic target for KMT2A-r ALL due to its predictive value because it contributes to leukemia invasiveness and CNS infiltration and more frequent CNS relapse [11,19]. The most common partner genes in AML in children under one year of age are AF9 (22%), AF10 (27%) and ELL 17%) [4,11]. KMT2A rearrangements are acquired in hematopoietic progenitor cells in the in the fetus, leading to rapid progression and clinical manifestations of progression and clinical manifestations of IL [12–14]. KMT2A-r in AML is associated with the monocytic differentiation of AML. Dysregulation of HOX genes is a common feature of AML [13]. In the regulation of hematopoietic development, HOX genes play a key role. Dysregulated HOX gene expression can result from chromosomal translocations involving upstream regulators such as KMT2A. Specific clinical trials for infant ALL are conducted by three major cooperative groups: Interfant (based in Europe), COG (based in North America) and the Japanese Pediatric Leukemia Study Group (JPLSG). All recently completed trials have used a prospective, risk-stratified approach including KMT2A-r status and age. In contrast to infants, patients older than 1 year have more favorable genetic features in the form of high hyperdiploidy and ETV6::RUNX1 fusion. Studies have shown that older children share cytogenetic abnormalities with KMT2A-g, albeit with a different distribution; the proportion of patients with favorable genetic risk (hyperdiploidy, ETV6::RUNX1) is higher (60% vs. 12% KMT2A-r). Next-generation sequencing (NGS) involves DNA, RNA or miRNA sequencing. NGS provides a tool for identifying the most important alterations in ALL that may help determine the prognosis and pathogenesis of the disease [14].

3.2. Clinical Features

Acute childhood leukemia often presents with typical leukemia symptoms such as bruising, bleeding, fever, asthenia, hepatosplenomegaly. As for patients with infant leukemia, they are characterized by more aggressive manifestations and early central nervous system involvement [1,9,15]. Thus, children under 1 year of age are characterized initially higher hyperleukocytosis, more significant risk of tumor lysis syndrome (TLS). In addition, IL often presents with skin infiltration (Blueberry Muffin Syndrome) and other extramedullary foci (Figure 1). Leukemoid skin infiltration are more characteristic of myeloid IL and occur in about two thirds of patients (common in FAB-M4 and FAB-M5 AML), whereas they are rare in lymphoblastic IL [8]. They are unique in that they can occur without peripheral blood or bone marrow involvement. Leukemoid skin infiltration is described as multiple papules and nodules of blue, red or brown color. This type of leukemia has a very poor prognosis. It is possible that the chemotherapy may not be able to penetrate the skin sufficiently, resulting in a higher rate of relapse in these patients.

These different clinical features of IL may be related to the stage of development, fetal hematopoiesis and its different origins. Also, to the peculiarities of infantile leukemia can be attributed: transformation of one type of leukemia into another, heavier tolerance of chemotherapy, more severe late complications of therapy (endocrine, cardiovascular, neurogenic).

3.3. Instrumental and Laboratory Diagnostics

As mentioned above, IL is characterized by an initially higher leukocytosis, reaching values with a WBC count >400,000 cells/μL. Acute leukemia is diagnosed when more than 20% of blast cells are present in a bone marrow puncture. There are specific morphological and immunophenotypic features in IL. FAB (French-American-British classifications) types are more characteristic of IL: M4, M7 (megakaryoblastic), M5 variant (monoblastic) [8]. Lymphoblastic IL are more likely to have the L1 subtype than the L2 subtype, and less likely to have the L3 subtype [9]. Immunophenotypic characterization of infant ALL and AML are distinct: KMT2A-r ALL are CD19- positive/CD10 negative and often no co-express one or more myeloid antigens, suggesting that they are of the nature of immature lymphoid-forerunners [10]. Infant leukemia patients can be of undefined a mixed

 doi:10.20944/preprints202508.1869.v1

phenotype (mixed phenotype acute leukemia) or lack of differentiation markers (acute undifferentiated leukemia). In the cytological examination of biopsy specimens from skin infiltrates, the presence of blast cells confirms the diagnosis of leukemia, even in the absence of blast cells in the bone marrow and in the peripheral blood [12]. Abdominal ultrasound reveals marked hepatosplenomegaly, the lower edge of the liver may reach the pelvic region.

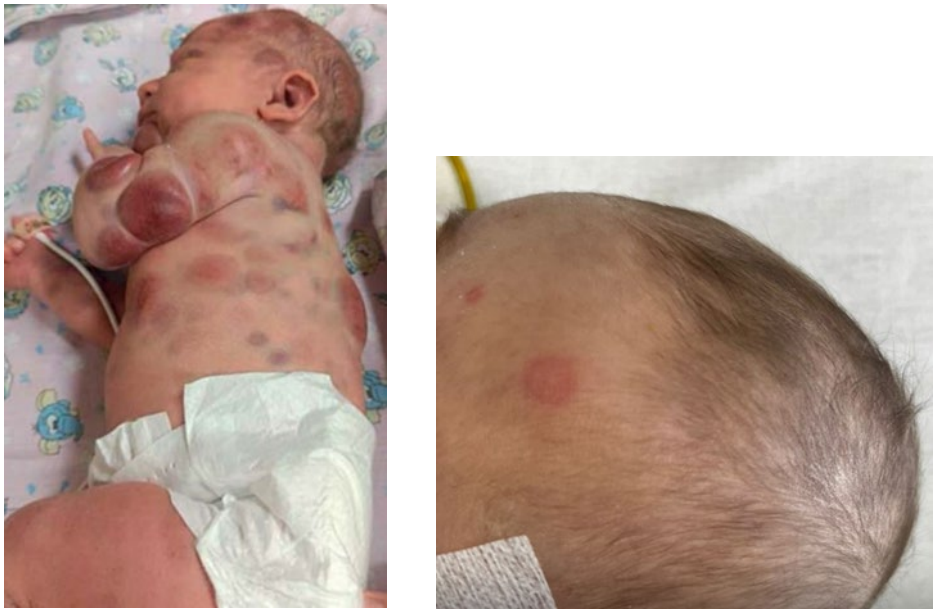

Figure 1. Leukemoid skin infiltration (own clinical case).

3.4. Treatment

The use of ALL and AML chemotherapy regimens or specific protocols for IL (Interfant-99/06), with the calculation of drug doses per kilogram of body weight, is unique in the treatment of IL. The use of intensive chemotherapy as well as allo-HSCT is not excluded by functional features of organs in children under 1 year of age. One of the challenging aspects of treating IL is the increased incidence of toxic and infectious complications during chemotherapeutic treatment, which is explained by the complexity of physiological processes during the first year of life [16,17].

There are currently three major groups focused on conducting clinical trials specific to IL: the Children's Oncology Group (COG), the Japanese Pediatric Leukemia/Lymphoma Study Group (JPLSG), and the Interfant Study Group [20].

The Interfant Study Group is the largest international organization that conducts research activities in the field of IL, involving various international research groups, including the BFM-group. Their study included 482 infants divided into standard and high-risk groups (based on response to 1 week of systemic prednisone) between 1999 and 2005. Factors associated with an adverse outcome included: age less than 6 months, KMT2A-r, poor response to weekly prednisolone prophase, CD10 negativity and initial hyperleukocytosis [21]. The two-year treatment protocol was based on a hybrid regimen that included elements used to treat both ALL and AML, while minimizing the use of anthracyclines. and alkylating agents. Only for high-risk patients was the option of allo-HSCT considered, if a compatible donor was available. Higher MRD (minimal residual disease) levels at the end of induction and consolidation were significantly associated with poorer disease-free survival. These studies demonstrated that MRD is an important prognostic factor and that its diagnosis is of added value for the identification of risk groups in children with ALL. MRD analysis may be useful in the decision-making process regarding allo-HSCT. Subsequently, another study was conducted in this group called Interfant-06, which differed from its predecessor by removing dexamethasone and vincristine during maintenance chemotherapy. However, the new treatment approach did not

 doi:10.20944/preprints202508.1869.v1

significantly improve outcomes for children with ALL - there was no significant difference in 6-year EFS when compared (46.1% in both protocols).

The COG trial, known as P9407, was designed to provide shortened but intensified therapy by eliminating age- and weight-based dose reductions for most chemotherapy drugs to improve EFS. In the P9407 results, toxicity mortality (mainly infectious) in the first 90 days of treatment was reported in 25% of 68 infants. After the study was modified prednisolone was changed to dexamethasone, the dose of daunorubicin was reduced - the early mortality rate dropped to 6% [22].

The Japanese Pediatric Leukemia/Lymphoma Study Group combined two protocols for the treatment of infant leukemia named MLL96 and MLL98. Between 1995 and 2001 102 patients with IL with and without KMT2A-r were included [23]. Patients with KMT2A-r in first remission after intensive chemotherapy were to receive allo-HCT from any available donor but this approach revealed a high incidence of early relapse. These studies demonstrated the benefits risk-adapted therapy according to KMT2A status, with outcomes being significantly better in patients without KMT2A gene involvement, 5-year EFS and OS of 95.5% [23,24]. The 5-year EFS and OS in patients with KMT2A were 38.6 % and 50.8 %, respectively.

In the analysis of the BFM treatment protocols BFM-98 and BFM-2004 for infant AML, the EFS was 43% in the KMT2A -r group and 52% without KMT2A -r [24,25]. Japan's Infant Leukemia Study Group in 2003 showed the results of treating infants AML with intensive chemotherapy alone and analyzed prognostic factors. Thirty-five patients with infant AML treated with intensive chemotherapy alone between 1995 and 1998 were included in this study. Induction therapy included etoposide, cytarabine and mitoxantrone. Four different courses of intensification therapy were then used, including etoposide, cytarabine and anthracyclines or vincristine. According to the results, 3-year OS and EFS were 76% and 72%, respectively. The study also shows that MRD levels by flow cytometry after consolidation therapy can be a predictor of AML outcome [26].

Also, individual case studies of treatment outcomes in myeloid IL have been reported in the literature. For example, in 2009 a group of European researchers reported their experience in treatment a patient with the M6 variant of infant myeloid leukemia. The treatment was carried out according to the MRC-12 protocol with age adjustment. Complete remission was achieved after 1 course of ADE (cytarabine, daunorubicin, etoposide). Treatment was complicated by several periods of febrile neutropenia and infections. The patient has now been in durable complete remission for 4 years [10,27].

Modern genetic studies are opening new avenues in the treatment of KMT2A -r IL through the introduction of new targeting drugs. This is most often used: proteasome inhibitors, hypomethylating agents (such as cytosine analogs azacytidine or decitabine), menin-KMT2A inhibitor, FLT3 inhibitors, curaxin CBL0137, histone deacetylase inhibitors, CAR- T-cell [16,17]. The use of monoclonal antibodies such as blinatumomab and inotuzomab ozogamicin are actively used in the treatment of patients with ALL of different age groups, including infants.

3.5. Role and Place of Allo-HSCT

The need for allo-HSCT in IL (particularly AML) remains controversial. The use of allo-HSCT in IL is always a subject of discussion due to contradictory data and peculiarities of this age category. On the one hand, a number of studies and guidelines point to the high aggressiveness and unfavorable prognosis of leukemia in infants, especially in the presence of KMT2A-r, which justifies the early use of allo-HSCT even in the first remission. Arguments in favor of early transplantation include the potential to achieve long-term remission, reduced risk of relapse, and data from individual protocols where survival was higher in transplanted patients.

On the other hand, critics draw attention to the extremely high risks of the procedure itself in children in the first year of life: unfavorable tolerability, high incidence of complications (infections, GVHD, organ failure) and transplant-related mortality risks. In addition, modern intensive chemotherapeutic protocols with optimal supportive care can already achieve remission in some

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patients, and the potential benefits of HSCT do not always outweigh the risks, especially in the absence of unfavorable genetic markers.

In 2015, The Japanese Pediatric Leukemia/Lymphoma Study Group published the results of treating 62 children with KMT2A -r ALL by a short course of intensive chemotherapy followed by early allo-HSCT for 4 months. The EFS and OS a were 43.2% and 67.2% respectively, which was significantly higher than the group of patients who received chemotherapy alone [28].

The results of the Interfant-99 study, which included 483 children with previously untreated ALL treated between 1999 and 2006, showed that allo-HSCT in first remission is a possible treatment strategy for intermediate-risk infant KMT2A -r ALL with high MRD [13]. All patients were stratified into 2 arms based on response to a 1-week prednisolone phase. All patients received a 5-week induction regimen (prednisolone, dexamethasone, vincristine, daunorubicin, L-asparaginase, low-dose cytarabine and intrathecal injections) followed by a 4-week consolidation regimen (high-dose methotrexate, 6-mercaptopurine, high-dose cytarabine, L-asparaginase and intrathecal injections) and 7 weeks of reinduction therapy (dexamethasone, 6-thioguanine, vincristine, daunorubicin, low-dose cytarabine, cyclophosphamide and intrathecal chemotherapy injections) [29]. Patients in the poor response to 7-day prednisolone group were indicated for allo-HSCT.

The BFM group recommended etoposide, busulfan and cyclophosphamide as the conditioning regimen. Meanwhile, total body irradiation (TBI) was strongly discouraged due to concerns about long-term side effects. Cyclosporine A was used for GVHD prophylaxis [29]. At a median follow-up of 5 years, the EFS rate for KMT2A -r ALL was only 38.6%, but this was an increase compared with previous studies. Furthermore, the results of a study using TBI during the conditioning regimen showed that of 14 infants with KMT2A -r ALL transplanted in first remission, 78.5% survived and only moderate distant endocrine and nervous system effects were observed [29,30].

More recently, the results of the Children's Cancer Group (CCG 1953) and Pediatric Oncology Group (POG 9407) studies on the treatment of infant ALL were presented, using a similar chemotherapy regimen and recommending allo-HSCT in KMT2A -r cases [31]. 5-year EFS rates were 50.9% in the transplant group and 48.7% in the nontransplant group, suggesting no clinical benefit from first remission HSCT in infants with KMT2A -r ALL [32,33]

The effect of allo-HSCT in infant AML is also still unclear, due to the lack of randomized trials. In early studies, allo-HSCT provided long-term survival in some cases of AML among infants. The Japan Infant Leukemia Group Study analysis included all cases of AML in infants less than 2 years of age treated between 1974 and 1995 [34]. The conditioning regimen and GVHD prophylaxis differed among patients. It has been shown that infants with AML receiving HSCT had a 5-year disease-free survival rate of 73% [34,35]. But allo-HSCT was used in only four patients, while the others received autologous HSCT.

The Pediatric Oncology Group also compared the effect of intensive induction chemotherapy followed by allogeneic or autologous HSCT for infants with AML - survival rates in the allo-HSCT and chemotherapy groups were better than in the autologous HSCT group (71% vs. 40%) [36]. It was demonstrated that a conditioning regimen containing busulfan, melphalan, and cyclophosphamide was most commonly used for infants with AML and was well tolerated, avoiding serious long-term effects [35,36]. Table 1 shows some more studies in the field of treatment of infant leukemia using allo-HSCT [45–52].

Differences in the results of research studies have led to discrepancies between research groups regarding the role of allo-HSCT in current infant protocols.

 doi:10.20944/preprints202508.1869.v1

Table 1. A compilation of research papers [45–52] Treatment results of IL according to current studies.

Study	Disease	Country	Period (y)	HSCT(n)	nonHSCT (n)	Results	Publication
Pui et al	ALL	USA and Europe	1983–1995	28	103	Chemotherapy EFS 23%, OS 33%; HSCT EFS 18%, OS 25%	Leukemia volume 17, pages 700–706 (2003)
Marco et al	ALL AML	Spain	1990–1998	22	0	5-y DFS for ALL 56%; 5-y DFS for AML 73%	Journal of Clinical Oncology Volume 18, Number 18(2000)
Sanders et al [51]	ALL	United States	1982–2003	40	0	3-y DFS overall 42%; 3-y DFS for HSCT in CR1 76%	Blood. 2005;105(9)
Murray et al	ALL	United States	1986–2005	4	5	HSCT OS 75%; chemotherapy OS 60%	Fetal Pediatr Pathol 2008
Jacobsohn et al	ALL	United States	1992–2005	16	0	4-y EFS 75%	Biol Blood Marrow Transplant. 2005
Isoyama et al	ALL	Japan	1995–1998	19	8	EFS HSCT 58%; EFS chemotherapy 63%	Br J Haematol. 2002
Chessels et al	ALL	UK	1992–1999	12	57	3-y EFS ≈35% for both HSCT and chemotherapy	Br J Haematol. 2002
Kosaka et al	ALL	Japan	1998–2002	29	15	3-y EFS HSCT in CR1 64%;3-y EFS overall 44%	Blood. 2004
Mann et al	ALL	International	1999–2006	37	240	4-y DFS HSCT 60%; 4-y DFS chemotherapy 47%	Blood. 2010
Dreyer et al	ALL	United States	1996–2000	53	47	5-y EFS HSCT 49%; 5-y EFS chemotherapy 49%	J Clin Oncol. 2011
Kawasaki	AML	Japan	1995–1998	2	26	EFS HSCT 100%; EFS chemotherapy 77%	Blood. 2001
Creutzig et al	AML	Germany	1998–2010	14	0	OS HSCT 93%	Leukemia. 2012
Pieters et al [46]	ALL	United States	2006 - 2024	111	494	4-year DFS after HSCT of 44.0%	J Clin Oncol 2019
Takachi T [45]	ALL	Japan	2019	43	13	13 pts relapsed after HSCT, 1 pt. died in CR, and 29 pts. are in CR	Blood Adv 2021
Parikh et al [48]	ALL AML MDS	International	2000 -2014	472	0	3-y OS overall 31% 3-y DFS after HSCT of 28%	JAMA Pediatr. 2019

3.6. Clinical Experience

Median follow-up was 23.5 months (IQR 11-47.2). OS after allo-HSCT in the group of infants with leukemia high-risk was 64%, in the group of patients with KMT2A-r - 66.6 % The relapse rate after allo-HSCT was 9%. The most common cause of treatment failure was infectious complications in the early post-transplant period. Grade I-II acute GVHD developed in 2 patients (18%) and grade III-IV in 3 patients (27%). Of those patients who are currently alive, 2 patients have chronic GVHD (extensive forms). Early relapse of leukemia occurred in two patients and they died. Primary graft failure was recorded in three patients, one of them required a second allo-HSCT. There are no serious long-term effects of allo-HSCT, surviving children develop in accordance with their peers (with the exception of two patients with c-GVHD).

 doi:10.20944/preprints202508.1869.v1

Table 2. Features of a group of infants with acute leukemia who received allo-HSCT.

Feature	Number of patients (n = 11)/100%
Type of acute leukemia	
AML	5 /54.5
ALL	4/27.2
MPAL	2/18.3
Sex distribution	
Male	6/54.5
Female	5/45.4
KMT2A-r	
Yes	6/54.5
No	5/45.4
CNS-status	
Positive	1/9
Negative	10/90.9
Stage of remission	
CR 1	6/54.5
CR 2	5/45.4
MRD status	
Positive	4/27.2
Negative	7/63.6
Novel drugs	
Blinatumomab	1/9
Inotuzumab ozogamicin	2/18.2
Nelarabin	1/9
Type of donor	
MMRD	5/45.4
MUD	5/45.4
MRD	1/9

4. Discussion

The problems of treating IL are multifaceted. Despite the development of genetic engineering, cellular technologies, the mortality rate of patients with IL remains at a high level. Effective chemotherapy requires dose modification due to factors affecting the pharmacokinetics of drugs differently than in other age groups, which is due to the peculiarity of infants hematopoiesis [37,38]. The toxic effects associated with treatment in both the early and late periods are problems that make the doses of chemotherapy to be reduced. Long-term complications that can occur after HSCT in infants are the result of both pre-transplant chemotherapy and radiation therapy aimed at the central nervous system. Many long-term complications in children have been associated with total body irradiation, and despite the fact that this treatment method shows great effectiveness in terms of myeloablation, physicians refrain from using it in children under one year old [47]. Infants who have undergone allo-HSCT are at a higher risk of experiencing severe adverse effects, including: interstitial pneumonia syndrome and sinusoidal obstruction syndrome. The risk of relapse in this population group is significant, and a deeper study of this problem will help in the future to inspect for new approaches in the management of such patients [48].

Many research groups noted late in the form of growth disorders of children's development, after treatment, especially with the inclusion of allo-HSCT [39–41]. The accession of severe infectious complications requires aggressive antimicrobial prophylaxis, even outside of neutropenia. Stratification into risk groups of acute lymphoblastic leukemia in infants depending on the presence

 doi:10.20944/preprints202508.1869.v1

of adverse factors. Based on pooled data from numerous studies, the principal prognostic factors include: patient age less than 6 months at diagnosis, presence of KMT2A-r, and failure to achieve morphological remission by day 14 [40]. It remains uncertain whether increasing the use of strategies such as HSCT during first remission, or intensifying current hybrid protocols that combine both lymphoid- and myeloid-targeted therapies, can improve cure rates for patients [41,42].

The experience of our center has demonstrated acceptable transplantation mortality and satisfactory OS results. Patients who received monoclonal antibodies before the HSCT stage showed the best results, while it did not matter which remission the patient was in before HSCT [43]. All patients had their MRD levels assessed by flow cytometry. Of the 4 patients with positive pre-HSCT MRD status, two were alive and two died (one from toxic complications, the other from early relapse) [44]. Two cases of primary graft failure were associated with severe infection in the early post-transplant period, and one patient with primary graft failure had to undergo secondary allo-HSCT with donor switch- he is alive and in remission now [43,44]. Few GVHD cases suggest that our GVHD prevention strategies are effective and safe.

Can we say unequivocally that allo-HSCT in all cases of infantile leukemia is strictly necessary, based on our clinical cases? Probably not. The fact that seven out of eleven patients who received HSCT are currently alive with no signs of leukemia speaks in favor of HSCT in children in this category. Against allo-HSCT, however, is the fact that some of the surviving patients suffer from c-GVHD - a condition that invalidates the child and can also cause death. Furthermore, two patients died in the early post-transplantation period due to specific HSCT complications; perhaps they would have survived using a standard chemotherapeutic approach

5. Conclusions

Infant leukemia is a rare but aggressive disease. KMT2A rearrangements are most common genetic abnormality in infant leukemia. The treatment of acute leukemia in infants is challenging and optimal protocols are being developed around the world specifically for these patients. Taking into account the characteristics of this age group, the choice of chemotherapy drug doses should be carefully considered and the indications for allo-HSCT should be balanced. With great progress in the last decade, it has become possible to perform the allo-HSCT phase with minimal toxicity and maximal efficiency. The use of monoclonal antibodies to induce remission before HSCT is a promising direction to reduce toxicity and increase survival in children with infant ALL. In summary, the introduction of allo-HSCT into the standards of treatment of IL should be strictly individualized: indications are determined not only by leukemia biology, but also by the infant's condition, donor availability, center resources, and parental preparation for possible complications. Better study and understanding of the genetics and biology of IL will stimulate the development of new therapeutic strategies to improve the quality of life of children in the future.

Author Contributions: Conceptualization, Kirill Kirgizov, Timur Valiev, Mihail Kiselevsky, Svetlana Varfolomeeva ; methodology, Irina Kostareva, Irina Shubina; software, Irina Kostareva, Nara Stepanyan, Nataliya Batmanova; formal analysis, Irina Kostareva, Mihail Kiselevsky.; resources, Irina Kostareva.; data curation, Irina Kostareva, Timur Valiev, Mihail Kiselevsky; writing— Irina Kostareva.; writing—review and editing, Timur Valiev, Mihail Kiselevsky, Kirill Kirgizov; visualization, Irina Shubina.; supervision, Kirill Kirgizov, Timur Valiev, Mihail Kiselevsky, Svetlana Varfolomeeva.; project administration, Kirill Kirgizov, Svetlana Varfolomeeva. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Conflicts of Interest: The authors declare no conflicts of interest.

 doi:10.20944/preprints202508.1869.v1

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