haematologica
Journal of the Ferrata Storti Foundation

Treatment of leukemic ocular infiltrations with intra-arterial chemotherapy in very early mixed relapse of B-cell acute lymphoblastic leukemia

by Marta Andrzejewska, Maksymilian Deręgowski, Zuzanna Anioł, Julia Dezor-Garus, Anna Stodolska, Sandra Rutkowska, Anna Przybyłowicz-Chalecka, Olga Zając-Spychała, Anna Gotz-Więckowska and Katarzyna Derwich

Received: January 10, 2026.
Accepted: March 2, 2026.

Citation: Marta Andrzejewska, Maksymilian Deręgowski, Zuzanna Anioł, Julia Dezor-Garus, Anna Stodolska, Sandra Rutkowska, Anna Przybyłowicz-Chalecka, Olga Zając-Spychała, Anna Gotz-Więckowska and Katarzyna Derwich. Treatment of leukemic ocular infiltrations with intra-arterial chemotherapy in very early mixed relapse of B-cell acute lymphoblastic leukemia.
Haematologica. 2026 May 7. doi: 10.3324/haematol.2026.300507 [Epub ahead of print]

Treatment of leukemic ocular infiltrations with intra-arterial chemotherapy in very early mixed relapse of B-cell acute lymphoblastic leukemia

Marta Andrzejewska[1,2], Maksymilian Deręgowski[1], Zuzanna Anioł[1], Julia Dezor-Garus[3], Anna Stodolska[1,2], Sandra Rutkowska[1], Anna Przybyłowicz-Chalecka[4], Olga Zając-Spychała[1], Anna Gotz-Więckowska[3], Katarzyna Derwich[1]

1. Poznan University of Medical Sciences, Department of Pediatric Oncology, Hematology and Transplantology, Institute of Pediatrics, Poznan, Poland
2. Poznan University of Medical Sciences, Doctoral School, Poznan, Poland
3. Poznan University of Medical Sciences, Department of Ophthalmology, Poznan, Poland
4. Department of Hematology and Bone Marrow Transplantation, Poznan University of Medical Sciences, Poland

Corresponding Author: Marta Andrzejewska, MD
Corresponding author email address: marta.andrzejewska@student.ump.edu.pl

Running title: Intra-arterial Chemotherapy for ALL Ocular Infiltration

Key words: ocular leukemic infiltration, acute lymphoblastic leukemia relapse, intra-arterial chemotherapy, pediatric acute lymphoblastic leukemia

Acknowledgements: We would like to express our sincere gratitude to the patient and the patient's family. We thank the entire clinical team involved in the patient's care, including physicians and nursing staff, for their dedication, professionalism, and invaluable contribution to the treatment process.

Conflict of interest: The authors declare that they have no competing interests.

Data availability: No data were generated during the preparation of this manuscript.

Author Contribution(s): Conceptualization: MA, ZA. Writing—original draft, investigation and data curation: MA, MD, AS, JDG, SR, APC. Writing—review and editing: MA, MD, ZA, SR, JDG, AS, SR, APC, OZS, AGW, KD. Final draft preparation: MA, ZA, MD, SR, ASS, SR, APC, OZS, AGW, KD. All authors have read and approved the final manuscript.

Funding Information: No external funding was acquired to facilitate the manuscript.

B-cell acute lymphoblastic leukemia (B-ALL) constitutes the most common pediatric neoplasm of excellent cure rates in the standard-risk group, with event-free survival (EFS) of approximately 93%[1]. Five percent of ALL patients have central nervous system (CNS) infiltration at diagnosis, as diagnosed by cytospin and imaging studies[2]. Still, roughly 20-30% patients have overt infiltration, which might be diagnosed with flow cytometry[3]. This technique is not yet routinely implemented in treatment protocols. Considering the close anatomical and biological relationship between the CNS and ocular structures, the eye may serve as a potential sanctuary site of disease. It is unclear whether retinal leukemic infiltration should be treated as CNS positivity; ophthalmological evaluation is not mandatory at diagnosis and is recommended only by selected ALL study groups, e.g. in European Standard Clinical Practice (ESCP) protocol. No standardized protocol for ophthalmological examination has been established; despite various ocular manifestations in leukemia patients, before and during treatment[4,5]. Treatment of ocular infiltration has not been standardized; only a few reports describe the use of standard chemotherapy protocols or orbital radiotherapy in a relapse setting[6,7].

Herein, we describe the treatment of a patient with very early mixed bone marrow-central nervous system relapse of B-ALL, with leukemic infiltration of the retina present from the primary diagnosis, who was successfully treated with intra-arterial chemotherapy and allogeneic hematopoietic stem cell transplantation (allo-HSCT) preceded by total body irradiation (TBI) with CNS boost. Additionally, the patients' leukemic blasts were characterized by *IGH::MYC* fusion, usually found in Burkitt's lymphoma. Patient's guardians consented to the use of the clinical data and their publication, and the study was performed in accordance with the Declaration of Helsinki and in respect of national ethical rules.

A twenty-month-old female patient was admitted with a suspected diagnosis of leukemia. Her medical history revealed frequent infections over the past two months. On examination, petechiae, hepatosplenomegaly, enlarged lymph nodes, and hematuria were noted. Laboratory results showed hemoglobin 8.6 g/dL, platelets 18,000/µL, and leukocytes 40,000/µL. B-ALL was diagnosed, with 37% blasts exhibiting the following phenotype: $CD10^{pos}CD19^{pos}CD20^{neg}CD22^{pos}TdT^{neg}cytCD79a^{pos}CD38^{pos}HLA\text{-}DR^{pos}CD34^{neg}cytIgM^{pos}CRLF2^{neg}kappa^{neg}lambda^{neg}$. CNS status was assessed as negative (1 leukocyte/µL in cerebrospinal fluid (CSF)). Karyotype analysis showed 47,XX,+i(1)(q10),t(8;14)(q24;q32) in all 21 analyzed metaphases, indicating an *IGH::MYC* fusion. A single-nucleotide polymorphism (SNP) array study revealed monoallelic deletions of *CDKN2A* and *CDKN2B*. Initial diagnostics included an ophthalmological evaluation, which revealed small and medium-sized intraretinal hemorrhages in both eyes' posterior poles and periphery. The brain magnetic resonance imaging (MRI) showed no abnormalities. The patient began treatment following the AIEOP BFM 2017 Poland protocol. Due to the development of a hematoma and a subsequent infection at the port site, chemotherapy on day 15 was delayed by five days. Minimal residual disease (MRD) was negative at day 15, and the patient was classified as early non-high-risk. She completed the entire protocol I up to day 64. Before starting protocol M, the patient was admitted with symptoms of apathy and vomiting.

Subsequent examinations revealed a very early mixed bone marrow-central nervous system relapse, with 6,060 leukocytes/µL in CSF, of which 99.9% were lymphoid blasts. 56% blasts were found in the bone marrow. The phenotypic characteristics were consistent with the initial diagnosis. The patient began treatment according to the IntReALL 2010 High-Risk protocol, arm A. Fundus examination revealed significant abnormalities. In the right eye (RE), the optic disc margins were blurred; in the left eye (LE), the disc was completely obscured by creamy masses. The peripapillary retinal nerve fiber layer was edematous with multiple

creamy, round foci, the largest measuring approximately two disc diameters (DD). In the RE, additional creamy masses were seen along the proximal segment of the temporal venous arcade. Repeated brain MRI showed no signs of leukemic infiltration. The patient responded well to the induction phase, with a negative MRD and CSF negative for leukemic blasts on flow cytometry. Fundus changes had almost completely resolved; however, six weeks later, subtle peripapillary infiltrates recurred (Figure 1). To ensure no evidence of leukemia by targeting the ocular infiltrations, and suitably prepare the patient for allo-HSCT, intra-arterial chemotherapy inspired by retinoblastoma protocols was discussed. Two cycles of chemotherapy administered directly to the ophthalmic artery were performed; the first cycle included a 0.5 mg topotecan injection into the right ophthalmic artery, and 0.5 mg topotecan and 4 mg melphalan into the left ophthalmic artery. The second cycle involved 0.5 mg topotecan and 4 mg melphalan for the left eye, and 0.5 mg topotecan and 30 mg carboplatin for the right eye. This approach led to the resolution of the leukemic infiltration.

The patient was eligible for an allo-HSCT from a matched unrelated donor (9/10 HLA match, with a mismatch at locus A; matched for blood group). MRD before transplantation was 0.002%. The conditioning regimen included a CNS boost (3 fractions of 2 Gy), 12 Gy total body irradiation (TBI), etoposide phosphate 60 mg/kg, and thymoglobulin 7.5 mg/kg. Complete donor chimerism was achieved on day +83. On follow-up post-allo-HSCT ophthalmic examination, the patient had exotropia and a relative afferent pupillary defect (RAPD) in the right eye (RE). Fundus examination showed retinal atrophy and occlusion of retinal vessels, with no signs of leukemic infiltration. The left eye (LE) was unremarkable (Figure 2). At subsequent follow-up, degenerative fundus changes progressed secondary to retinal vascular occlusion and hypoxia, with neovascularization developing in both the anterior and posterior segments of the RE, leading to neovascular glaucoma and vitreous hemorrhage. After treatment with intraocular pressure (IOP)-lowering medications and an intravitreal anti-VEGF injection (ranibizumab), the condition of the right eye stabilized. At the last follow-up visit, visual acuity was no light perception in the RE and 6/6 in the LE. The patient remains under close ophthalmic monitoring. She has been in remission for more than one year after allo-HSCT.

To the best of our knowledge, this is the first case report of ALL with ocular and CNS involvement treated with intra-arterial chemotherapy with retinoblastoma-inspired protocol, targeting ocular leukemic infiltrations. Previous reports show the efficacy of using intravitreal methotrexate to treat ocular leukemia[8]. In our case, despite a good MRD response and clearance of blasts from the CSF, progressive fundus infiltration was observed, raising concerns about treatment efficacy in ocular sanctuary sites and an adequate patient's preparation to allo-HSCT. Historically, extramedullary ocular involvement in ALL has been rare and has been associated with a poor prognosis. Patients were treated with orbital radiotherapy and a standard chemotherapy backbone, and sometimes allo-HSCT[9]. This report shows the possible efficacy of additional chemotherapy in advanced ocular involvement. The use of intra-arterial chemotherapy via direct catheterization of the ophthalmic artery provided targeted delivery to the ocular vasculature, achieving high local drug concentrations at the sites of leukemic infiltration, while limiting systemic exposure. Such approach led to complete resolution of leukemic infiltrates in both eyes, warranting no evidence of leukemia and demonstrating its therapeutic efficacy in carefully selected case. However, the therapy was associated with significant ocular toxicity. The patient developed retinal atrophy, likely related to intra-arterial chemotherapy, followed by neovascular complications. These ultimately resulted in irreversible vision loss in one eye. The observed findings raise concerns about the long-term ocular safety profile of this treatment, despite its well-established use in intra-arterial

chemotherapy protocols for retinoblastoma[10]. There is a growing body of evidence of melphalan's ocular toxicity, especially in pigmented eyes (which were present in the patient), and possible development of cataracts, retinal and vascular complications[11]. Bearing these in mind, the ultimate goal was to prepare the patient accordingly to allo-HSCT, providing the best possible CNS and ocular control. This was achieved, and the complications developed after allo-HSCT, ultimately raising concern of additive CNS boost and TBI impact on the overall toxicity profile.

Earlier reports describing ALL with ocular involvement do not characterize the disease immunologically and genetically. In our patient, leukemic blasts were of pre-B immunophenotype (cytIgM^{pos}CD10^{pos}CD34^{neg}TdT^{neg}), suggesting a switch to a more mature form of ALL. The immunophenotype does not meet the criteria for Burkitt leukemia, as CD20 and sIgM kappa/lambda are negative, indicating a late pre-B ALL phenotype, rather than a Burkitt leukemia phenotype, as CD34 and TdT are also negative[12]. Genetic changes observed in cases of pre-B ALL with IGH::MYC, as reported in the literature, were associated with positive TdT expression, suggesting this is the first negative case of its kind[13].

The leukemic blasts were positive for t(8;14)(q24;q32), which leads to *IGH::MYC* rearrangement, and confers a more aggressive course of the disease. It is characteristic of Burkitt lymphoma or L3 ALL. Notably, the presence of the isochromosome 1, i(1)(q10), is also worth mentioning, as it is nonspecific for ALL but is associated with disease aggressiveness[14]. *CDKN2A/B* deletions are recurrent in pediatric ALL and are linked with poor prognosis and early relapse, as seen in this patient[15]. The genetic profile, particularly the presence of *IGH::MYC*, raises the question of whether this case represents a biologically distinct subtype of B-ALL or a leukemia with features overlapping Burkitt leukemia/lymphoma, which may require tailored therapeutic strategies.

This report contributes to the evolving understanding of how to effectively treat extramedullary involvement in an aggressive form of ALL, characterized by uncommon genetic findings.

References:

1. Pieters R, de Groot-Kruseman H, Van der Velden V, et al. Successful Therapy Reduction and Intensification for Childhood Acute Lymphoblastic Leukemia Based on Minimal Residual Disease Monitoring: Study ALL10 From the Dutch Childhood Oncology Group. J Clin Oncol. 2016;34(22):2591-2601.

2. Thastrup M, Duguid A, Mirian C, et al. Central nervous system involvement in childhood acute lymphoblastic leukemia: challenges and solutions. Leukemia. 2022;36(12):2751-2768.

3. Thastrup M, Marquart HV, Schmiegelow K. Flow Cytometric Detection of Malignant Blasts in Cerebrospinal Fluid: A Biomarker of Central Nervous System Involvement in Childhood Acute Lymphoblastic Leukemia. Biomolecules. 2022;12(6):813.

4. Nazzicone K, Kim R, Fine A, et al. Ocular involvement in newly diagnosed pediatric leukemia: A systematic review and meta-analysis. Pediatr Investig. 2025;9(2):150-159.

5. Shahriari M, Shakibazad N, Haghpanah S, et al. Extramedullary manifestations in acute lymphoblastic leukemia in children: a systematic review and guideline-based approach of treatment. Am J Blood Res. 2020;10(6):360-374.

6. Chocron IM, Morrison DG, Friedman DL, et al. Ophthalmic manifestations of relapsing acute childhood leukemia. J AAPOS Off Publ Am Assoc Pediatr Ophthalmol Strabismus. 2015;19(3):284-286.

7. Sahdev I, Weinblatt ME, Lester H, et al. Primary Ocular Recurrence of Leukemia Following Bone Marrow Transplant. Pediatr Hematol Oncol. 1993;10(3):279-282.

8. Vishnevskia-Dai V, Sella King S, Lekach R, et al. Ocular Manifestations of Leukemia and Results of Treatment with Intravitreal Methotrexate. Sci Rep. 2020;10(1):1994.

9. Pflugrath AE, Brar VS. Bilateral optic nerve and retinal infiltration as an initial site of relapse in a child with T-cell acute lymphoblastic leukemia. Am J Ophthalmol Case Rep. 2020;18:100695.

10. Han JW, Lee CS, Hahn SM, et al. The Efficacy of Alternate Systemic Intravenous Chemotherapy and Intra-arterial Chemotherapy Approach for Eye Globe Salvage in Retinoblastoma. Cancer Res Treat. 2023;55(1):270-278.

11. Liao A, Hsieh T, Francis JH, et al. Toxicity and Efficacy of Intravitreal Melphalan for Retinoblastoma: 25µg vs 30µg. Retin. 2021;41(1):208-212.

12. Sharma M, Sachdeva MUS, Varma N, et al. Characterization of immunophenotypic aberrancies in adult and childhood acute lymphoblastic leukemia: A study from Northern India. J Cancer Res Ther. 2016;12(2):620.

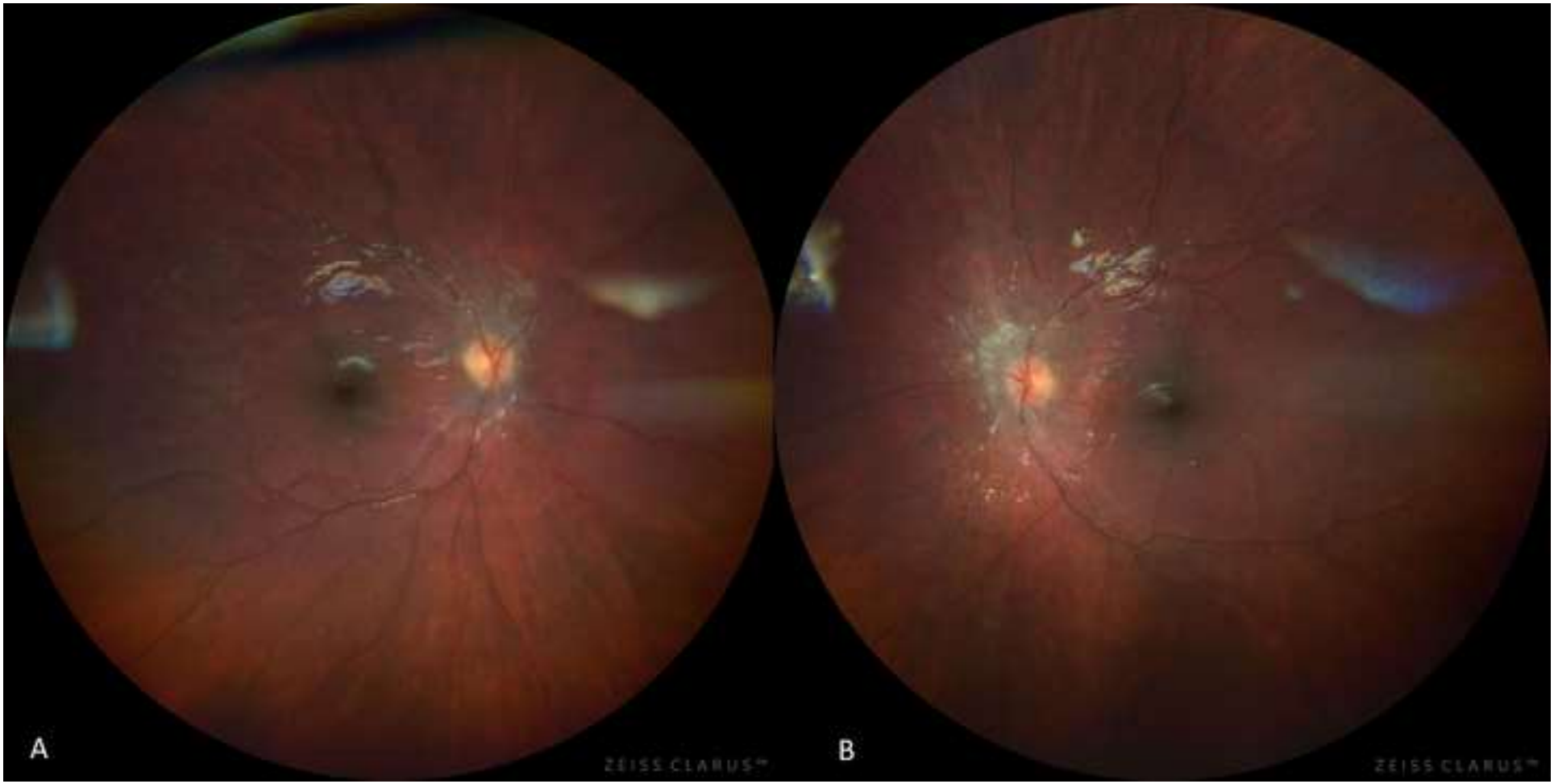
13. Wagener R, López C, Kleinheinz K, et al. IG-MYC+ neoplasms with precursor B-cell phenotype are molecularly distinct from Burkitt lymphomas. Blood. 2018;132(21):2280-2285.

14. Rim JH, Kim HS, Shin S, et al. Isochromosome 1q in Childhood Burkitt Lymphoma: The First Reported Case in Korea. Ann Lab Med. 2015;35(6):663-665.

15. Feng J, Guo Y, Yang W, et al. Childhood Acute B-Lineage Lymphoblastic Leukemia With CDKN2A/B Deletion Is a Distinct Entity With Adverse Genetic Features and Poor Clinical Outcomes. Front Oncol. 2022;12:878098.

Figure 1: The pictures of eye fundi obtained with a Zeiss Clarus camera 6 weeks after the initiation of the relapse treatment. Panel A shows the right eye fundus, while panel B left eye fundus – both with recurring subtle leukemic infiltrates around both optic discs.

Figure 2: The pictures of eye fundi obtained with a Zeiss Clarus camera before the start of conditioning regimen. Panel A shows the right eye fundus, in which retinal atrophy and occlusion of retinal vessels are seen. Panel B left eye fundus, which is unremarkable for any pathologic changes.


A
ZEISS CLARUS™
B
ZEISS CLARUS™


A
ZEISS CLARUS™
B
ZEISS CLARUS™