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Very late relapse of ALL after 14 years: treatment with CAR-T cells

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Definitions of the time point of relapse of acute lymphoblastic leukemia (ALL) in children include very early, early, and late. Very early is diagnosed if it occurs <18 months after primary diagnosis and <6 months after completion of primary therapy; early relapse is diagnosed if it occurs ≥18 months after primary diagnosis and <6 months after completion of primary therapy; and late relapse is diagnosed if it occurs ≥6 months after completion of primary therapy. Cases of late relapse which are diagnosed ≥5 years after initial diagnosis have been reported only rarely. There is no exact definition of very late relapse of ALL. It was proposed by Vora et al. [1] to define very late relapse (VLR) as those occurring >10 years from the day of complete remission (CR); the incidence of VLR was c.1% in a large cohort of de novo ALL [1]. Aldoss et al. [2] showed that mutation profiles tested by a next generation sequencing (NGS) panel in available paired cases differed between the primary diagnosis and a relapse occurring >5 years afterwards; this did not support a clonal relationship, thereby indicating distinct genetics between the original and late relapse of ALL. Recent data shows that 5-year leukemia-free survival (LFS) and overall survival (OS) in children with VLR are 56% and 63% respectively; most children receive allogeneic hematopoietic cell transplantation (allo-HCT) [2].

We here report the case of a patient with VLR occurring almost 14 years after the primary diagnosis, with a first very early relapse. The patient had already reached a cumulative dose of anthracyclines, and additionally could neither tolerate most chemotherapy, nor HCT.

A 3-year-old girl from a first pregnancy, born in good condition (Apgar score 9), was hospitalized in 2009 due to fever. Laboratory tests showed leukopenia, anemia, thrombocytopenia, and elevated levels of lactate dehydrogenase. Acute lymphoblastic leukemia was diagnosed [pre-B-common+ phenotype; SR group; no central nervous system (CNS) involvement]. Oncological treatment was implemented according to the ALL-IC-BFM-2002 scheme. On day 33, M1 marrow was aplastic. During treatment, numerous episodes of prolonged neutropenia and liver toxicity were noted, and frequent respiratory infections. Prior to the start of the mM protocol, severe myeloid relapse ALL (group S4) was diagnosed and treated according to the ALL-REZ-BFM-2002 protocol. Therapy was complicated by pneumonia and liver toxicity. The patient was qualified for allogeneic bone marrow transplantation from a compatible unrelated donor, which was performed in 2010. The patient remained in remission, with post-transplant chimerism of the donor.

The patient was re-admitted to the department almost 14 years after the first diagnosis. A second isolated recurrence of acute lymphoblastic leukemia with the same pre-B-common+ phenotype as in the previous diagnosis was found. At the time of relapse, the patient had cachexia

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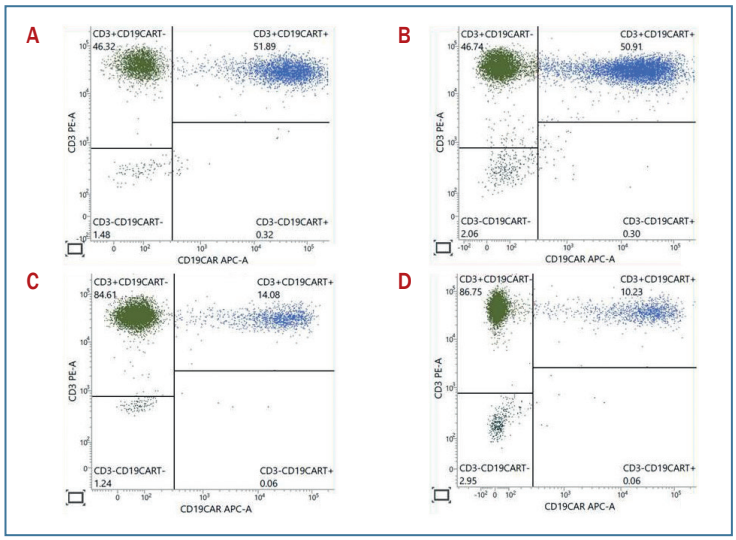

Figure 1. Expression of chimeric antigen receptor T-cell (CAR-T) cells in peripheral blood after infusion of tisagenlecleucel: **A.** Day 4; **B.** Day 8; **C.** Day 18; **D.** Day 24

[weight and height deficit below the 3rd percentile, body mass index (BMI) = 12]. Over the past decade, the patient was expected to have been covered by multi-specialist care encompassing gastroenterology, neurology, rehabilitation (posture defects, muscle contractures), ophthalmology (myopia), and endocrinology (short stature, primary amenorrhea, lack of sexual maturation). However, control visits had not been carried out for several years. Due to cachexia, poor appetite, and low body weight, a gastroscopy was performed, which revealed features of gastroparesis and secondary malabsorption syndrome.

Due to a high risk of inability to withstand the intensive cycles of chemotherapy used in protocols for relapsed ALL, the induction of treatment according to the AIEOP-BFM--2017-Poland program was started. Due to the features of myocardial insufficiency in echocardiography examination, a decision was made to conduct treatment without anthracyclines. On the 8th day of treatment, 3% of blasts were found in a peripheral blood smear. On the 15th day, 11% of lymphoblasts were found in a myelogram [flow cytometry minimal residual disease (FC MRD) 5.21%]. On day 33, we found remission of underlying disease and FC MRD negative, although MRD polymerase chain reaction (PCR) was positive ($<1 \times 10^{-4}$). Treatment was complicated by a *Candida dubliniensis* blood infection and invasive pulmonary mycosis, requiring combined antifungal therapy (caspofungin and amphotericin B, followed by isavuconazole, after which a temporary improvement in the general condition was obtained). Periodically, signs of circulatory and respiratory insufficiency, signs of inflammation, and kidney function imbalance were observed. Due to a positive direct antiglobulin test (DAT) result, systemic steroid therapy was additionally used in the treatment.

After meeting the required criteria, the girl was qualified for the implementation of chimeric antigen receptor T-cell (CAR-T) therapy for the following reasons: second relapse, relapse after HCT, and contraindications for second HCT due to marginal organ capacity. Bridging chemotherapy was applied according to FRALLPOST 2004 with the use of vincristine and polyethylene glycol (PEG)-asparaginase. Nonetheless, MRD by PCR ($<1 \times 10^{-4}$) before CAR-T therapy was present. On 22 June, 2023 a preparation of autologous modified T lymphocytes (CAR-T; tisagenlecleucel) was transfused. Cytokine release syndrome (CRS) grade 1 occurred, and there were no signs of neurotoxicity. During the early post-infusion phase (<30 days), a very high expression of CAR-T cells was present, reaching >50% of all lymphocytes (Figure 1). A myelogram (day +26) showed complete remission and, for the first time, MRD was absent in the PCR examination. As anemia and thrombocytopenia persisted, the patient was qualified for treatment with eltrombopag and erythropoietin. There were no viral reactivations. The patient remains in a good general condition. She achieved a weight gain of >10% within the first month after the end of therapy.

In conclusion, in this pediatric patient with VLR-ALL, suffering from many comorbidities and partial contraindications for chemotherapy and HCT, it was possible to obtain CR, although with the presence of MRD-PCR.

Preparation for, and therapy with, CAR-T was performed; a large number of CAR-T cells were present in peripheral blood in the early post-infusion period, resulting in MRD--PCR negativity.

Therapy with CAR-T represents a new therapeutic possibility in patients with advanced refractory or relapsing ALL or non-Hodgkin lymphoma (NHL) [3–6].

Authors' contributions

JS — design of study. MRP, KC, RD, AM, ED — clinical data. JS, MRP, KC — writing manuscript. MK, BKR, RD — laboratory analysis. EM, HM, KG, MRP, ŁL — CAR-T handling. JS, MRP, KC — critical review. All authors — final approval.

Conflict of interest

The authors declare no conflict of interest.

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Ethics

The work described in this article has been carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans; EU Directive 2010/63/EU for animal experiments and uniform requirements for manuscripts submitted to biomedical journals.

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