Case Report

Insights in Blood Disorders

Near-Early T-Cell ALL with Overexpression of BAALC and BCL-2 Genes, Non-Responsive to High-Dose Chemotherapy and Hematopoietic Stem Cell Transplantation, but with Impressive Response to Venetoclax

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ABSTRACT

Clinical and laboratory data are presented of a 29 year female patient with BAALC- and BCL-2-positive T-cell acute lymphoblastic leukemia developed from early leukemic progenitors which was treated unsuccessfully with high-dose chemotherapy and allogeneic stem cell transplant (allo-HSCT), but revealed an impressive effect of venetoclax. For reasons beyond our control, allo-HSCT with myeloablative fludarabine-busulfan (14 mg/kg) conditioning regimen was performed at the peak of relapse when blast count in bone marrow aspirate was 77.5%, whereas level of BAALC-expressing earlier progenitors (EP) reached 186%. HSCT was ineffective, since the number of blasts on day+30 reached 86%, whereas the burden of BAALC-expressing EP decreased to the cutoff values. Later, at post-transplant stage, an impressive response to venetoclax coupled with hypomethylating agent was observed. Following allo-HSCT and combined venetoclax therapy a severe pancytopenia developed, which required the second transplantation of peripheral blood stem cells from her haplo-matched father. After transplantation hematopoietic recovery started on day 10+. Although bone marrow aspirate at this point was hypo cellular, it contained all types of granulocytic and erythroid elements and 2.2% of blasts only.

Keywords

Near-Early adult T-ALL, *BAALC*+, BCL-2+, Hyperdiploid karyotype, Resistance to therapy, Response to venetoclax.

Introduction

T-cell acute lymphoblastic leukemia in adults is considered to be rare disease with inferior response linked with *BAALC*-overexpression and complex karyotypes with ≥3 cytogenetic alterations per metaphase [1,2]. Meanwhile, there is evidence, that early variant of T-ALL is characterized by high expression of gene *BCL-2* and, hence, can be treated successfully with venetoclax [3-7]. It has been also shown, that T-ALL patients with higher levels of *BAALC* expression are more likely to have early T-ALL (P<0.0001) and CD34 positivity (P<0.0001). Meanwhile, the patients with high *BAALC* had an inferior relapse-free survival (RFS, P=0.0008) and overall survival (OS, P=0.0001). Furthermore, rate of complete remission achievement in this cohort of patients was inferior, whereas cumulative incidence of relapses (CIR) was much higher and did not depend on whether HSCT was carried out or not. Four-year OS and EFS rates in patients with increased vs normal level of *BAALC* expression, were 18% *vs* 58% (P=0.0001) and 21% vs 85%) (P=0.0008), respectively [1]. Recent data show that all abovementioned clinical and laboratory parameters are greatly improved in a case of high-dose risk chemotherapy followed by allogeneic hematopoietic stem cell transplantation (allo-HSCT), which was performed in remission [6,7].

Herein, we report a case of positive response to venetoclax of adult *BAALC*- and *BCL-2*-positive near early T-ALL resistant

to both high-dose chemotherapy and allo-HSCT, but responded impressively to post-transplant venetoclax therapy combined with hypomethylating agents.

Clinical Case Description

A 29-year-old female presented in March 2021 with a history of systemic lymph node enlargement and hepatomegaly. An affected cervical lymph node was excised, and histological examination was performed. At microscopy, lymph node structure appeared completely effaced, due to massive proliferation of medium-sized lymphoid cells with blast morphology and high mitotic index. Immunohistochemistry showed strong positivity for TdT, CD7, CD3, bcl-2 and moderate positivity for CD5 and c-myc in nearly all cells. Moreover, nearly all cells were moderately positive for Pax-5 and, although somewhat heterogeneously, for CD19. CD34 appeared positive in more than 25% cells. Few cells (<10%) were CD33-positive. CD79a, CD22, myeloperoxidase, CD117 as well as CD4, CD8, CD1a, PD-1, CD20, Cyclin D1 tested negative (Figure 1). Bone marrow aspirate (22.04.21) contained 60.8% blast cells with immunophenotype as follows: CD45dim/SSC low, CD7 +, CD2+, CD34+, CD38+, sCD3-, CD4-, CD8-, CD1a-, TCR-, CD117-, CD33-. CD19-, cytCD3+, MPO-, cytCD79a-. Taking into account unequivocal CD5 positivity of blast cells proven by immunohistochemistry, these findings were considered consistent with diagnosis of near-early T-ALL [6,7]. Cytogenetic analysis (22.04.21) revealed hyperdiploid in half out of 20 analyzed metaphases with the following karyotype: 2n=50-52, XX, +8, +10, +11, +14.

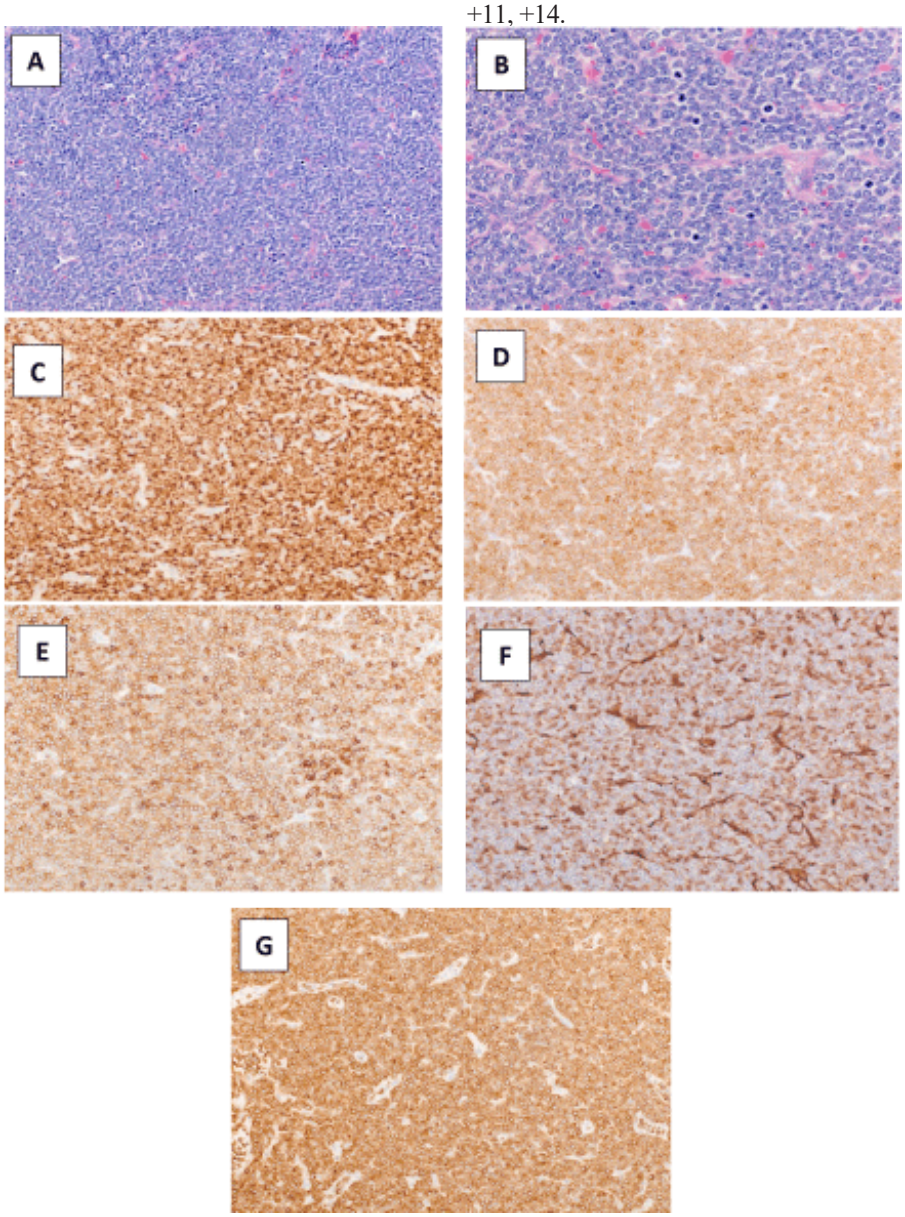

Figure 1: Near-ETP ALL. Lymph node biopsy. A: HE, x100, B:HE, x400, C-G: Immunoperoxidase, x200. **A.** Lymph node structure is effaced by proliferation of lymphoid cells with blastic features. **B.** Sheets of blast cells with round or slightly irregular nuclei, open chromatin with small nucleoli and scant cytoplasm. High mitotic activity. **C.** TdT expression in all neoplastic cells. **D.** Moderate CD3 expression in all neoplastic cells. **E.** CD5 expression in >75% of neoplastic cells. **F.** CD34 expression in ca. 25% of neoplastic cells. **G.** Uniform expression of bcl-2 in all neoplastic cells.

The first chemotherapy course according to the HyperCVAD + asparaginase protocol started on 26.04.21. As a result, the blast count in bone marrow aspirate decreased to 7%.

The 2nd similar course (20.05.21) did not also result in complete remission. Therefore, a search for unrelated bone marrow donor was initiated. Morphologic and cytogenetic remission was achieved only on 24.06.21, but lasted for a short time. Relapse with 75.5% blasts in the bone marrow sample developed prior to allo-HSCT. In addition, higher levels of *BAALC* and *WT1* genes (156% and 9633 copies, respectively) were detected. Despite complex clinical situation, a decision was made to perform salvage allo-HSCT from partially compatible (9/10) matched non-related donor without an attempt to achieve a novel remission or improvement of hematopoiesis. On 7.12.21 after myeloablative conditioning with FLU and BU 14mg/kg, 2.38x10^6/kg of body weight CD34$^+$bone marrow cells were transplanted with minimal success. The study of bone marrow sample obtained soon after transplantation revealed 86% of immature blast cells, although the level of *BAALC* expression dropped to the cutoff values (25%) (Figure 2). The blast content was decreased after a course of combined therapy with venetoclax and azacitidine therapy (100 mg/day each for two weeks).

Since the patient developed secondary hypocellularity of bone marrow, the repeated HSCT from haploidentical related donor was performed on 28.01.2022. The total number of transplanted CD34$^+$ peripheral blood progenitors was >8x10^6/kg of body weight. On 1.04.22, the bone marrow aspirate proved to be normocellular without blast elements, showing restoration pattern of all basic haematopoietic lineages. This finding was associated with minimal levels of *BAALC* (2%) and *WT1* (10 copies/10^4 ABL gene).

Discussion

Our study demonstrates the expected resistance of adult *BAALC*-positive hyperdiploid variant of near-e-T-ALL to both high-dose chemotherapy and allo-HSCT. The latter was performed unfortunately at the peak of relapse with high blast count and increased level of *BAALC* expression. Following the first HSCT, the number of blasts and BAALC-expressing earlier porogenitors (EPs) changed in different ways. Whereas the number of immature blasts post-transplant increased to 86%, the number of BAALC - expressing EPs reached cutoff levels.

As recently shown by our group [8-10], the level of *BAALC*-expression in patients with AML, measured by means of RT-qPCR, reflect the approximate numbers of *BAALC*-expressing

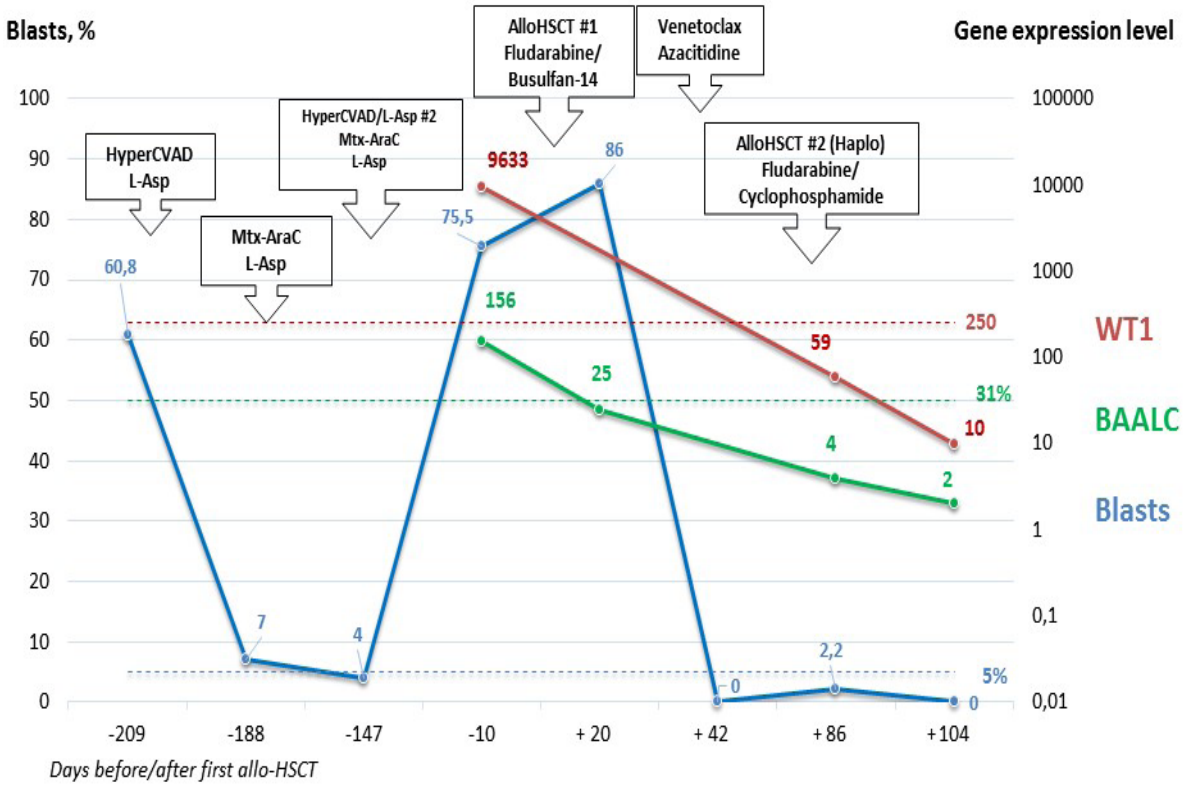

Figure 2: Time course of molecular changes in patient with near-early T-ALL who was subjected to allo-HSCT from partially (9/10) matched non-relative donor. The transplant was performed at relapse, with 77.5 % of blast cells in bone marrow and highly increased expression of *BAALC* (186%) and *WT1* genes (9639 copies). On D+20 post-transplant, the level of *BAALC* expression declined to the cutoff levels, but the number of marrow blasts increased to 86%. Their content was decreased after a course of combined therapy with venetoclax and azacitidine therapy (100mg/day each). Since the patient developed secondary hypocellularity of bone marrow, a repeated HSCT from her HLA-haploidentical father was performed on the Day+86 after the 1st allo-HSCT.

ELPs. Hence, one may suggest that normalization of *BAALC* expression in our patient with near-e-T-ALL at posttransplant stage may be directly linked with response to myeloablative conditioning regimen which appears to be completely ineffective if assessed by the blast counts. Meanwhile, the blast population was completely lost from the bone marrow after short course of venetoclax therapy. Hence, one may expect that treatment by venetoclax at pretransplant stage in this category of atients would be also effective, as demonstrated in several recent studies [11-20]. Our observation supports the idea [12] that venetoclax may be useful when preparing for HSCT in bcl-2-positive ALL. We have demonstrated that myeloablative conditioning regimen is effective with regard to *BAALC*-expressing EPs, at least in the near-e-T-ALL case. Meanwhile, the bone marrow blasts were insensitive to conditioning regimen applied. Hence, a conclusion may be drawn which links general efficiency of HSCT in therapy-resistant cases with achieving maximal effect of venetoclax or some other targeted drugs which must be consolidated with respect to *BAALC*-expressing population of ELPs using a myeloablative conditioning regimen. This effect should be monitored in patients with *BAALC*-positive acute leukemias by means of RT-qPCR-based evaluation of *BAALC*-levels which, in our opinion, may reflect the numbers of *BAALC*-expressing ELPs. Since elevated levels of *BCL-2*, along with near-e-T-ALL, may be also present in some AML patients, and even, in B-ALL cases, this parameter, like as *BAALC*-expressing ELP numbers, should be also checked systematically, in order to use therapeutic potential of venetoclax for both controlled preparation for HSCT in *BAALC*-positive leukemias, and for treatment of post-transplant relapses.

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