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BCL2 Antagonist Venetoclax Combined with Non-Aggressive Chemotherapy in Treating Fatal TCF3-HLF Positive Acute Lymphoblastic Leukemia

Wang P, He Y, Wang J, Ye Q, Zhang H and Zhang W**

Department of Hematology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, China

Abstract

TCF3-HLF-fusion positive Acute Lymphoblastic Leukemia (ALL) is very rare and nearly incurable according to current standard chemotherapy even with hematopoietic stem cell transplantation. Optimized treatment strategies are urgently needed. In this report we present two cases with TCF3-HLF fusion with different therapeutic regimens and review ever reported cases in literature. We proposed that combination of BCL2 antagonist venetoclax with non-aggressive chemotherapy should be considered for this fatal subtype ALL in the future.

Keywords: TCF3-HLF; Acute lymphoblastic leukemia; BCL2 antagonist venetoclax; Non-aggressive chemotherapy

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Correspondence:
Weina Zhang, Department of Hematology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, 510623, China, Tel: +86-020-38076060; Fax: +86-020-38076060; E-mail: ZWN18@126.com
Hui Zhang, Department of Hematology, Guangzhou Women and Children's Medical Center, Guangzhou Medical University, Guangzhou, 510623, China, Tel: +86-020-38076060; Fax: +86-020-38076060; E-mail: zhanghuirjh@gwcmc.org

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Introduction

Acute Lymphoblastic Leukemia (ALL) is the most common malignancy in children. With the optimization of combined chemotherapy and Hematopoietic Stem Cell Transplantation (HSCT) under appropriate circumstances, more than 85% cure rate has been achieved [1]. The prognosis of ALL patients varies considerably among distinctive genetic subtypes [2,3]. For example, newly patients diagnosed with the DUX4 and ETV6-RUNX1 fusions have utmost excellent prognosis with a five-year survival rate exceeding 95% [4]. In contrast, TCF3-HLF fusion gene, resulting from the rare translocation of t(17;19) (q22; p13), defines a special subtype with a disappointed dismal prognosis [5]. Though HSCT is regarded as the last chance for this subpopulation, successful long-term survival cases are rarely reported. Thus, new treatment regimens are in urgent needed to improve the outcome of ALL patients with TCF3-HLF genetic alteration. Because of extremely low incidence, only a few case reports sprinkled in the body of literature. In this study, we report TCF3-HLF cases enrolled onto CCCG-ALL-2015 (ChiCTR-IPR-14005706) with different outcome treated with two distinctive strategies. We also summarize the treatment and prognostic information in a sum of 49 TCF3-HLF positive cases from ever-reported literature and this research, highlighting the importance of BCL2 inhibitors combined with non-aggressive chemotherapy.

Case Series

Case 1

An 11-year old girl present with paleness and fatigue was diagnosed with B-ALL through bone marrow morphological and immunophenotypic assays in March 2018. Leukemic cells were staggered at the pre-B stage expressing CD19, CD79a and cytoplasmic Immunoglobulin heavy-chain μ (Igμ). Karyotyping analysis demonstrated the translocation of chromosome 17 to chromosome 19 and TCF3-HLF fusion was further verified by real-time PCR using cDNA as template. Consistent with previous reports, she also had coagulation disorder depicted by significantly prolonged Prothrombin Time (PT) and low fibrinogen. Initially, she received her induction chemotherapy according to the CCCG-ALL-2015 protocol for intermediate risk with the combination of dexamethasone/prednisone, poly (ethylene glycol) -asparaginase (PEG-ASNase), daunorubicin and vincristine (Figure 1). The Minimal Residual Disease (MRD) level for day19 was 2.2%. Through two cycles of further induction chemotherapy including CAT (cyclophosphamide, cytarabine and 6-mercaptopurine) and augmented CAT (two doses of vincristine weekly and PEG-ASNase once supplemented to CAT), however, the MRD level jumped to 26.6%. After one cycle of consolidation treatment through High Dose of Methotrexate (HDMTX), the MRD level increased to 40.4%. An integrated treatment was given including bortezomib (1.3 mg/m^2 for three doses every three days),

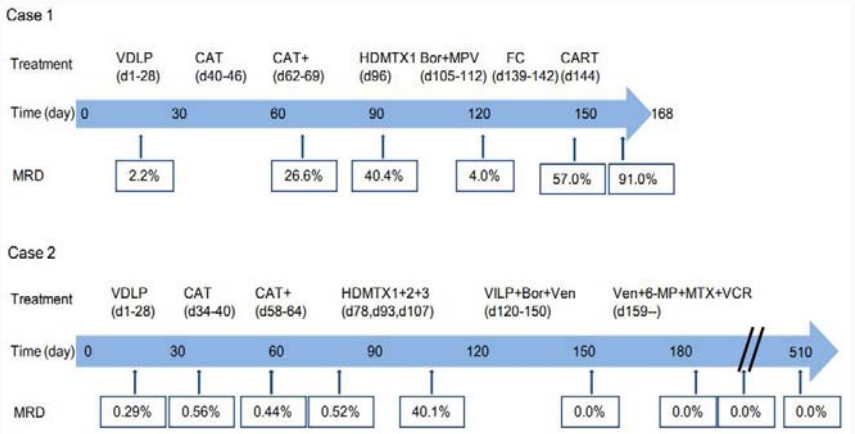

Figure 1: Main treatment regimens and MRD levels at different time points for the two cases.
VDLP: Vincristine, Doxorubicin, PEG-ASNase and dexamethasone/prednisone; CAT: Cyclophosphamide, Cytarabine and 6-Mercaptopurine; CAT+: CAT Supplemented with Vincristine and PEG-ASNase; HDMTX: High Dose of Methotrexate; Bor: Bortezomib; MPV: Mitoxantrone, Dexamethasone and Vindesine Sulphate; FC: Fludarabine and Cyclophosphamide; VILP: Vincristine, Idarubicin, PEG-ASNase and Dexamethasone; Ven: Venetoclax; 6-MP: 6-Mercaptopurine; MTX: Methotrexate; VCR: Vincristine

mitoxantrone (10 mg/m^2 once), dexamethasone (20 mg/m^2 for five days) and vindesine sulfate (3 mg/m^2 for two doses weekly). This induction stage treatment was complicated by neutropenia with fever and meropenem was used for anti-infection. The bone marrow then showed a detectable MRD level 4%. In view of the persistent of leukemic cells, we next conducted anti-CD19 Chimeric Antigen Receptor (CART) cell therapy. After a pretreatment with fludarabine and cyclophosphamide, engineered CART cells were transfused into her body. Unfortunately, she developed Cytokine Release Syndrome (CRS) presenting with constant high fever, headache, high blood pressure and waist pain. The interleukin 6 monoclonal antibody tocilizumab was used to control CRS. Though the symptoms of CRS were alleviated, the bone marrow evaluation showed 91% blast cells. This patient died 168 days after her initial diagnosis.

Case 2

A three-year old girl present with fever and hematuria was admitted to emergency room in September 2019. Coagulation function test showed obviously increased PT and Partial Thromboplastin Time (APTT) and low fibrinogen level. The myelogram displayed ninety-one percent's leukemia blasts and forty-five percent in her peripheral blood. Flow cytometry determined the B-cell origin expressing CD19, CD79a, CD10, but not Igμ. Targeted gene capture and sequencing identified the existence of TCF3-HLF fusion gene as well as a NRASG13D mutation. The same induction and consolidation regimens to case #1 were applied to her (Figure 1). Due to severe breathing difficulties and poor mental response considering aggravating infection, she was transferred to intensive care unit for one week's respiration support and anti-infection treatment. During induction, plasma, cryoprecipitate, fibrinogen and platelets were transfused to correct coagulation abnormalities. The MRD levels of day 19, day 33 and day 46 were 0.29%, 0.56% and 0.44%, respectively. At the same time, the transcript of TCF3-HLF fusion gene was always positive through Real-Time quantitative PCR (RT-qPCR). As expected, after subsequent two cycles of consolidation treatment with HDMTX, she experienced relapse with the MRD level 40.1%. Further gene analysis identified the retainment of both TCF3-HLF fusion gene and NRAS G13D mutation. In April 2020, we initiated a REL-ALL-2017 based re-induction therapy namely VILP, including vincristine (1.5 mg/m^2 weekly for one month), Idarubicin (8 mg/m^2 twice), PEG-ASNase (2000 IU/m^2 twice) and dexamethasone (8 mg/m^2 daily for the beginning three days and 6 mg/m^2 for the next 28 days). The proteasome inhibitor bortezomib (1.3 mg/m^2 weekly twice) and BCL2 inhibitor venetoclax (mainly 50 mg/d for three weeks) were co-administrated with the VILP regimen. During the time, she had a granuloma for a long time and subsequent bacteremia. *Enterococcus faecium* were cultured positive in her blood and also *Streptococcus oralis*, *Pseudomonas aeruginosa* in her Peripherally Inserted Central Catheter (PICC). Antibiotics including vancomycin and imipenem were used to manage this serious septicopyemia. After this cycle of modified re-induction, she obtained complete remission with an undetectable MRD by both multi-flow cytometric assay and RT-qPCR assay. In following treatment, we skipped the two cycles of consolidation of REL-ALL-2017, and took an optimized maintenance therapy including 6-mercaptopurine (50 mg/m^2 daily), methotrexate (25 mg/m^2 weekly), and venetoclax (50 mg daily). Monthly vincristine and quarterly PEG-ASNase were applied according to schedule. Intrathecally injection with dexamethasone, methotrexate and cytarabine was administrated monthly to prevent central nervous system leukemia. She does not get HSCT because of family reason, yet she is healthy now with durable complete remission at both morphological and molecular level within a follow up of one year.

Discussion

According to previous classification criteria, TCF3-HLF fusion gene was not listed as a marker for high risk stratification. Accumulated data show that all patients of this genotype have extremely poor prognosis with poor responses to induction therapy or relapse early [6]. Though intensive therapy may help to improve the treatment outcomes within most patients based on past experience, all cells with TCF3-HLF fusion are not sensitive to conventional chemotherapeutic drugs schemed in induction regimen as compared to those with TCF3-PBX1 fusion [7,8]. In Table 1, we retrospectively reviewed 49 TCF3-HLF positive all cases with survival data, from which we can draw the conclusion that traditional chemotherapy did not benefit these patients. Since the capacity of multiple chemotherapeutic drugs seems to be exhausted, Hematopoietic Stem Cell Transplantation (HSCT) may be the last chance for patients with TCF3-HLF fusion. However, substantial relapses are also observed in HSCT patients after MRD-negative remissions in TCF3-HLF-positive ALL [5,8,9].

Table 1: Clinical data of 49 patients with TCF3-HLF positive acute lymphoblastic leukemia.

ID	Ref	Age	Gender	WBC (10^9/L)	HSCT	Additional treatment	Outcome
1	this study	11.5	Female	31.1	No	CD19-CART	Died due to disease progression
2	this study	3.2	Female	24.7	No	Ven	ACR
3	[10]	15	Female	<20.0	No	No	Relapsed and died due to disease progression
4	[11]	67	Male	9.2	No	No	Induction failure and died due to disease progression
5	[12]	13	Female	13.8	Yes	Bli	ACR
6	[12]	14	Female	6.15	Yes	Bli	ACR
7	[12]	8	Male	14.49	Yes	Bli	ACR
8	[12]	7	Female	5.26	Yes	Bli+Ven	Died of infection under remission
9	[12]	10	Male	4.6	No	Bli+Ven+Dasatinib	Died of infection under CD19 negative relapse
10	[12]	3	Female	NA	Yes	Bli+Ven	Relapsed and died of infection
11	[12]	8	Female	11.3	Yes	Bli	ACR
12	[12]	5	Female	25.7	Yes	Bli	ACR
13	[12]	7	Male	8.2	No	Bli	ACR
14	[9]	25	Male	NA	Yes	Bli	Under re-induction therapy in trial with blinatumomab, complicated by tonic-clonic seizures
15	[8]	16.5	Male	14.3	No	No	Died from treatment-related complication
16	[8]	14.5	Female	2.2	No	No	Died from treatment-related complication
17	[8]	14.1	Male	6.3	Yes	No	Relapsed and died
18	[8]	13.8	Male	5.8	No	No	Relapsed and died
19	[8]	15.5	Male	20.3	Yes	No	Relapsed and died
20	[8]	12.7	Female	5	Yes	No	Relapsed and died
21	[8]	18.2	Female	5.2	Yes	No	Relapsed and died
22	[8]	14.7	Male	NA	No	No	Relapsed and died
23	[8]	3.4	Male	4.2	Yes	No	Relapsed and died
24	[8]	13.6	Male	3.4	Yes	No	ACR
25	[8]	14.3	Female	6.1	Yes	No	Relapsed after HSCT
26	[8]	14	Female	4.4	No	No	Induction failure
27	[5]	3	Female	8.4	No	No	Relapsed and died due to disease progression
28	[5]	14	Female	13.6	Yes	No	Relapsed and died of infection under re-induction
29	[5]	16	Male	6	No	No	Continuous MRD positive and died of infection
30	[13]	10	Male	10.9	No	Dasatinib	Relapsed and died of multiple organ system failure
31	[14]	10	Male	6	No	No	In second remission after CNS leukemia relapse
32	[15]	8	Male	NA	Yes	No	ACR
33	[16]	1.9	Female	<25	No	No	Relapsed and died due to disease progression
34	[16]	12.6	Male	22	Yes	No	Relapsed and died of HSCT related complications
35	[17]	10	Male	NA	No	No	Relapsed
36	[18]	5.6	Female	1.1	No	No	Relapsed and died due to disease progression
37	[18]	5.8	Female	88.6	No	No	Relapsed and died due to disease progression
38	[18]	14	Male	3.5	No	No	ACR
39	[19]	14	Female	4.2	Yes	No	Relapsed and died of infection under HSCT
40	[20]	14	Female	24.1	NA	NA	Died
41	[20]	12	Female	90	NA	NA	Died
42	[21]	12	Female	9.2	No	No	Relapsed and died
43	[22]	4	Male	NA	No	No	Relapsed and died due to disease progression
44	[23]	17	Female	NA	Yes	No	Relapsed and died due to disease progression
45	[23]	11	Male	NA	No	No	Induction failure and died due to disease progression
46	[23]	13	Male	NA	Yes	No	Relapsed and died due to disease progression
47	[24,17]	17	Female	NA	NA	No	Died
48	[25]	16.9	Male	11.8	NA	No	Died
49	[25,17]	15.5	Female	4.3	NA	No	Died

Ven: Venetoclax; Bli: Blinatumomab; ACR: Alive and Complete Remission; MRD: Minimal Residual Disease; NA: Not Available

Building upon these lessons, novel treatment regimens should be designed for trial. The TCF3-HLF oncogenic fusion protein has been proved to immortalize hematopoietic progenitors through regulating BCL2, an anti-apoptotic oncoprotein [26]. Previous transcriptome data in TCF3-HLF ALL cohort also suggested high expression of the BCL2 and TCF3-HLF ALL is extremely sensitive to the BCL2 antagonist venetoclax in xenograft model [8,27]. Venetoclax has been used in many clinical trials of relapsed/refractory hematological malignancies, such as multiple myeloma, chronic lymphocytic leukemia, acute myeloid leukemia and T-Cell acute lymphoblastic leukemia, indicating its safety and efficacy in this tough type of leukemia [28-30]. From our two cases, intensified chemotherapy did not benefit in newly diagnosed as well as in relapsed patients. Intriguingly, adding venetoclax to case #2's induction regimen significantly improved the treatment response identified by flow cytometry and quantitative PCR results. A long-term anti-leukemia effect of venetoclax was also identified in case #2's subsequent therapy even we abandoned intensive chemotherapy. In the re-induction phase, case #2 went through prolonged bone marrow suppression and septicemia; however, it was manageable through strong anti-infection support. Very recent report also demonstrated the feasibility of venetoclax and navitoclax, an orally bioavailable BCL-XL/BCL-2 inhibitor, in combination with chemotherapy in patients with relapsed/refractory B-cell and T-cell acute lymphoblastic leukemia [31]. Together with the evidence from related literatures, our cases pointed to the benefit of adding venetoclax for TCF3-HLF bearing cases. In addition, immunotherapy targeting CD19 through CART or bispecific T cell engager antibody blinatumomab has been attempted to treat this leukemia type. Recently, Mouttet' work supports application of CD19- directed immunotherapy combined with stem cell transplantation in treating TCF3-HLF positive ALL [12]. In this report, all nine patients achieved molecular remission after blinatumomab treatment. Blinatumomab is a bispecific T-cell engager antibody can bridge CD3-positive cytotoxic T cells and CD19-positive B cells, and its impressive responses rely on the homogeneous expression of CD19 on cell surface [32]. In our two cases we found the intensity of CD19 on cell surface is in a gradually increasing pattern, which hinted the possibility of inefficacy as well as CD19 negative relapse. We tried CD19-CART for case #1; however she suffered continuous elevated leukemic burden and eventually death. Even that, as the results of blinatumomab in this TCF3-HLF-positive all cohort are encouraging, the application of immunotherapy could be tried more in future. Pre-BCR signaling inhibitor dasatinib was used in two TCF3-HLF cases [12,13]. Dasatinib, targeting re-BCR downstream signaling molecules, such as SYK and BTK, has been showed anti-leukemic effects in pre-BCR positive ALL type including TCF3-HLF and TCF3-PBX1 *in vitro*, whereas Fischer et al. [13,33,34] challenged its sensitivity in TCF3-HLF-positive ALL [8]. Both the two patients treated with dasatinib had died because of relapsed disease. *In vitro* study showed TCF3-HLF-positive cells were sensitive to poly (ADP-ribose) polymerase inhibitors (olaparib and veliparib), while the result was failed to reproduce in mouse model *in vivo* [35]. At the same time, basic studies focusing on the transforming mechanism such as methylation profiling and interacting molecules are ongoing [36,37].

In conclusion, TCF3-HLF fusion is an extremely poor indicator of all. Except for standard chemotherapy, additional personalized treatment options should be also taken consideration for trial to improve their outcome. The approach that BCL2 inhibitor venetoclax combined with non-aggressive chemotherapy will have to be validated in more clinical studies.

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