Genetic Profile and Clinical Implications of PDGFRB Fusion in Adult B-Cell Acute Lymphoblastic Leukemia: A Retrospective Analysis

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Research

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Abstract

Background: To investigate the pathogenesis, genetic changes, treatment and prognosis of adult B-cell acute lymphoblastic leukemia (B-ALL) with platelet-derived growth factor receptor B (*PDGFRB*) fusion.

Methods: Clinical characteristics, treatment process and prognosis of 7 adult B-ALL patients with *PDGFRB* fusion were presented respectively, and the *PDGFRB* fusion was confirmed by fluorescence in situ hybridization, RNA sequencing and Polymerase Chain Reaction.

Results: 7 adult B-ALL patients with *PDGFRB* fusion were presented respectively. There were 5 males and 2 females, with a median age of 21 (range, 17-39) years and a median white blood cell count of 7.85 (range, 2.30-111.25) $\times 10^9/L$. The fusion partners were *EBF1*, *SMIM3* and *TERF2*. Three of 7 cases received tyrosine kinase inhibitor (TKI) targeted therapy, and 4 of 7 cases received chimeric antigen receptor T-cell (CAR-T) therapy. A total of 6 (85.71%) cases underwent haploid hematopoietic stem cell transplantation (Haplo-HSCT). Overall response rate was 71.43% (4/7), and the common adverse reactions during induction were febrile neutropenia and nausea. Seventy-five percent (3/4) and 100% (6/6) of patients were minimal residual disease negative after CAR-T and Haplo-HSCT. To the last follow-up, 2 of 7 cases relapsed in 2 and 7 months after remission, respectively, and the estimated 36 months of Event-free survival and Overall survival was 75.0% and 66.7%.

Conclusions: intensive therapy combined with CAR-T or TKI is needed to achieve deep remission, and sequential Haplo-HSCT may improve the prognosis of adult B-ALL with *PDGFRB* fusion.

Background

Disease progression remains a primary cause of mortality in B cell acute lymphoblastic leukemia (B-ALL), especially for Philadelphia-like (Ph-like) ALL, a high-risk subtype of B-ALL.¹ Owing a similar gene expression profile of Philadelphia chromosome-positive (Ph+) ALL, Ph-like ALL is associated with poor prognosis.² Allogeneic hematopoietic stem cell transplantation (allo-HSCT) was recommend and may improved this poor outcome.³ Fusion of platelet-derived growth factor receptor B (*PDGFRB*) has been emphasized in myeloproliferative neoplasms, and has become a therapeutic target of tyrosine kinase inhibitor (TKI).⁴ However, belonging to the ABL-class of fusion kinase category of Ph-like B-ALL, the fusion oncogene of *PDGFRB* are rarely reported in B-ALL.⁵ *PDGFRB* rearrangement in conventional karyotype examination is prone to low detection rate and missed diagnosis,⁶ and a rather proportion of B-ALL with *PDGFRB* rearrangement were refractory to conventional therapy.⁷ Given that patients with *PDGFRB* fusions are amenable to targeted therapy of TKI,⁸ it is necessary to identify these patients by using a comprehensive screening strategy. To provide a better comprehension of the clinical and pathological features, we performed a retrospective observational study in 7 cases of B-ALL with *PDGFRB* fusion in the First Affiliated Hospital of Soochow University.

Method

Patients and Study design

This was a retrospective, observational and descriptive study in the First Affiliated Hospital of Soochow University, which was approved by Ethics Committee of hospital, and informed consent form was provided by all patients. From 2015 to 2020, a total of 423 patients were diagnosed as Philadelphia chromosome-negative (Ph-) B-ALL in our center. 7 cases of which (1.6%) were found with *PDGFRB* fusion, and included in our study. The diagnosis of ALL with *PDGFRB* fusion was based on morphology, immunotyping, chromosome karyotype, molecular genetics and detection of somatic mutation (illumina nextseq550). Polymerase Chain Reaction (PCR), fluorescence in situ hybridization (FISH) and RNA sequencing (RNA seq, novaseq 6000) were integrated as the methods for testing *PDGFRB* fusion.

Treatment protocols

Induction chemotherapy: IVP (Idarubicin, Vincristine and Prednisone)-like regimen, such as VILP (L: L-Asparaginasum/pegaspargase), VDCP (D: doxorubicin, C: Cyclophosphamide), CIVP and VDLP was executed as the treatment protocols of induction therapy. Only one case (case 3) received the regimen of hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone (Hyper-CVAD)-A,⁹ and another case (case 5) took Dasatinib orally for inductive treatment (Table 2). The minimal residual disease (MRD) was analyzed in the bone marrow by flow cytometry (Beckman Coulter Ireland, Navios, Flow 10-color antibody panels). Consolidation regimen: Consolidation chemotherapy was based on high-dose methotrexate (MTX) and cytarabine (Ara-C),¹⁰ and 3 cases were combined with TKI therapy (Table 2). Chimeric antigen receptor-modified T cell (CAR-T) therapy: CAR-T cells were derived from autologous lymphocyte. Production of CAR-T cell was described in detail according to the previous report.¹¹ Allogeneic hematopoietic stem cell transplantation (Allo-HSCT): The conditioning regimen for patients received Allo-HSCT was modified BUCY (semustine, cytarabine, busulfan, and cyclophosphamide, BuCy).¹² All patients received the transfusion support of umbilical cord blood (UCB) pre-transplantation.¹³ Cyclosporin A, short-term methotrexate, and mycophenolate mofetil were used for graft-versus-host disease (GvHD) prophylaxis.¹⁴ Moreover, Anti-Thymocyte Globulin (ATG, Genzyme, Cambridge, MA, USA) was also administrated in vivo at 2.5 mg/kg on days -5 to -2 for preventing GvHD after haploidentical allo-HSCT.

Definitions and evaluations

Definition: Complete remission (CR), partial remission (PR), and relapsed disease were defined according to 2017 ELN recommendations.¹⁵ Overall response rate (ORR) was defined as (CR + PR)/ (all of the patients). Negativity or remission of MRD was defined as a level of MRD lower than 0.0001. CR without MRD (CRMRD-) was defined as CR with negativity by multiparametric flow cytometry (MFC). CR with MRD (CRMRD+) was defined as CR with positivity by MFC.

Cytokine Release Syndrome (CRS) and Neurologic Toxicity was graded respectively according to the consensus.¹⁶ The methods of diagnosis and treatment for acute GVHD (aGVHD) and chronic GVHD (cGVHD) were previously described in detail.^{17, 18, 19}

Results

Patients' characteristics

The characteristics of 7 patients with *PDGFRB* fusion were showed in Table 1, including 5 males and 2 females, with a median onset age of 21 (range, 17 to 39) years. There were 5 cases of initial diagnosis and other 2 cases of recurrence ALL. The median white blood cell (WBC) count at diagnosis was 7.85 (range, 2.3 to 111.25)×10⁹/L, and median platelet count was 51 (range, 28 to 191)×10⁹/L. The fusion partners were *EBF1* (n=4), *SMIM3* (n=1), *TERF2* (n=1) and only 1 case with a unknown partner gene. For patients with *EBF1-PDGFRB* fusion, corresponding mutations were found with *BCORL1* germline mutation, and somatic mutation of *PAX5* and *RUNX1*, respectively. Case 3 was combined with *SMIM3/PDGFRB* fusion and *TP53* somatic mutation. 4 of 7 cases showed anemia and most of patients (6/7) presented as normal karyotype at diagnosis. No eosinophils were found in bone marrow morphology, and there was no 5q31-33 rearrangement in karyotype in all patients (Table 1).

Table 1. Clinical data for *PDGFRB* fusion patients

	Sex	onset age (y)	Diagnostic state	WBC×10 ⁹	HB(g/L)	PLT×10 ⁹	BM: blasts%	FCM: blasts%	Method	Fusion type	mutant gene	chromosome
1	F	17	preliminary	7.9	70	45	51.5	86.3	PCR	<i>EBF1/PDGFRB</i>	<i>BCORL1</i> Germline mutation	normal
2	M	39	relapse	47.3	143	28	90.0	90.9	PCR FISH	<i>EBF1/PDGFRB</i>	<i>PAX5</i> mutation	normal
3	M	21	preliminary	2.3	76	45	87.5	87.8	RNA-seq	<i>SMIM3/PDGFRB</i>	<i>TP53</i> mutation	normal
4	M	21	preliminary	11.3	120	185	52.0	71.8	RNA-seq	<i>EBF1/PDGFRB</i>	<i>RUNX1</i> mutation	abnormal*
5	F	26	preliminary	111.3	56	51	90.0	76.2	RNA-seq	<i>TERF2/PDGFRB</i>	negative	no metaphase
6	M	20	preliminary	2.4	73	172	91.5	55.7	PCR	<i>EBF1/PDGFRB</i>	NK	normal
7	M	28	relapse	4.6	131	191	6.0	55.7	FISH	<i>PDGFRB</i> fusion	<i>IKZF1-IK6</i> transcribed isomers	normal

F, female; M, male; NK, not known; WBC, white blood cell count; HB, hemoglobin; PLT, platelet; BM, bone marrow; FCM, flow cytometry.*48-49XY[48]+19[48]+mar2[48]inc[cp2]/46,XY[48]

Response and Adverse Events of Induction Therapy

Of 7 patients, the overall rate of early response was 42.86% (3/7, Table 2). To 33 days after induction therapy, ORR was 71.43% (3 cases with CRMRD-; one case with CR and unknown MRD status), the CR rate at the end of induction therapy was only 57.14% (4/7). For case 1, 4 and 5 without CR after initial induction therapy, reached CR after plus chemotherapy, CAR-T, dasatinib plus chemotherapy, respectively. The common adverse events during induction chemotherapy were febrile neutropenia (2/7,28.57%), oral mucosal hemorrhage (1/7,14.29%), nausea (3/7,42.86%), and vomiting (1/7,14.29%). No patients died from induction chemotherapy. The median time of CR was 33 (range, 7 to 85) days, and the median time of MRD negative was 33 (range, 18 to 139) days.

Consolidation, Relapse and Survival

Three cases undertook a comprehensive therapy combined with TKI; TKI was administrated after CR for case 1, after MRD- for case 2, and in the middle of induction chemotherapy for case 3, respectively. Four cases received CAR-T therapy (2 for eliminating MRD, and 2 for re-induction therapy) and 6 cases underwent allo-HSCT from haploid-related donors. The recurrence rate was 28.57% (2/7). Case 2 and 7 experienced disease recurrence before allo-HSCT, with 2 and 7 months from CR to relapse, respectively. Both cases 3 and 6 were treated with Hyper CVAD A/B in consolidation therapy. The patients were followed up until January 30, 2021, and a median follow-up time was 29 (range, 7 to 72) months. Case 7 died of infection after allo-HSCT, with a persistent positivity of MRD. The estimated 36 months of Event-free survival (EFS) and Overall survival (OS) was 75.0% and 66.7%. (Table 2, Figure 1, Figure 2)

Table 2. therapy and survival data for *PDGFRB* fusion patients

	Induction	14d	33d	Time of CR (d)	Time of MRD-(d)	targeted therapy	CAR-T	HSCT	Months to Relapse(m)	Status(moths)
1	VILP	NR	NR	85	never	Imatinib	Yes	No	NA	loss to follow-up
2	VDCP	PR	CR _{MRD-}	33	33	Dasatinib	Yes	Yes	2	Alive (16)
3	Hyper-CVAD A	CR _{MRD-}	CR _{MRD-}	7	18	No	No	Yes	NA	Alive (29)
4	VILP	NR	NR	77	110	No	Yes	Yes	NA	Alive (37)
5	CIVP+ Dasatinib	NR	PR	61	139	Dasatinib	Yes	Yes	NA	Alive (7)
6	VILP	PR	CR _{MRD-}	29	29	No	No	Yes	NA	Alive (72)
7	VDLP	NK	CR	33	NK	No	No	Yes	7	Died of infection (32)

V, Vincristine; D, daunorubicin; L, L-asparaginase/pegaspargase/Pegaspargase; P, prednison; C, cyclophosphamide; I, Idarubicin; NR, non-remission; NK, not known

Treatment of CART

A total of 4 patients were infused with CAR-T cells for re-induction or eliminating MRD (Figure 1, Table 3). Case 2 was successfully infused with anti-CD19CD22 ($5 \times 10^6/\text{kg}$), while other 3 patients (case 1,4,5) received the therapy of anti-CD19 ($5 \times 10^6/\text{kg}$) CAR-T cells. Grade 2 of CRS appeared in 2 of 4 patients. Three cases (3/4, 75%) achieved MRD remission after CAR-T treatment. A persistent positivity of MRD was presented in case 1, with a 0.001 level of MRD. Bridging transplantation was performed in case 2, 4, 5 after CAR-T treatment. Allo-HSCT was not performed because there was no donor available for case 1 (Table 3).

Table 3. CAR-T data for *PDGFRB* fusion patients

	Relapse before CART	Status before CART	Blasts before FC%	CART source	Target	cell quantity $\times 10^6/\text{kg}$	CRS	therapeutic effect	Bridging transplantation
1	No	CR _{MRD+}	0	Autologous	CD19	5	2	CR _{MRD+}	0
2	Yes	NR	37	Autologous	CD19CD22	10	2	CR _{MRD-}	1
4	No	PR	7	Autologous	CD19	5	0	CR _{MRD-}	1
5	No	CR _{MRD+}	0	Autologous	CD19	5	0	CR _{MRD-}	1

Allo-HSCT

A total of 6 patients underwent Allo-HSCT from haploid-related donors (Haplo-HSCT). A total of 3 cases underwent CART bridging transplantation, and case 2 received CAR-T therapy as re-induction therapy before transplantation. Case 7 underwent Hyper-CVAD, VDCP, VTCP, AAG (cytarabinside + acracycin + G-CSF) regimen and did not achieve CR, and then received Salvage transplantation. The median time was 5.5 (range, 4-16) months from diagnosis to transplant. Side effects were mainly for the mild skin GVHD (grade 1) and diarrhea. No cases have disease recurrence after transplantation. Table 4.

Table 4. Haplo-HSCT data for *PDGFRB* fusion patients

	CAR-T	relapse	Status before HSCT	Diagnosis to HSCT time (m)	stem cell source	MNC ($10^8/\text{Kg}$)	CD34+ ($10^6/\text{Kg}$)	Neutrophil engraftment (d)	Platelet engraftment (d)	complication	Post-HSCT MRD level	relap of post-HSCT
2	Yes	Yes	CR2 _{MRD-}	6	CB+PB	7.05	2.97	11	12	GVHD skin	0×10^{-4}	No
3	No	No	CR1 _{MRD+}	6	CB+BM	3.3	1.518	11	13	GVHD skin	0×10^{-4}	No
4	Yes	No	CR1 _{MRD-}	4	CB+BM+PB	11.48	3.77	12	13	diarrhea	0.1×10^{-4}	No
5	Yes	No	CR1 _{MRD-}	5	CB+PB	5.44	5.02	12	12	No	0×10^{-4}	No
6	No	No	CR1 _{MRD-}	5	CB+BM+PB	10.2	2.04	10	11	No	0×10^{-4}	No
7	No	Yes	NR	16	CB+BM	9.48	2.75	12	12	GVHD skin	0×10^{-4}	No

CB, cord blood; BM, bone marrow; PB, peripheral blood

Discussion

The *PDGFRB* gene located at chromosome 5q32/5q33 is a member of the receptor tyrosine kinase family.^{7,20} The occurrence of chromosomal microdeletions during *PDGFRB* fusion resulted in difficult identification and missed diagnosis in routine chromosome karyotype analysis, which was also confirmed by the fact that no abnormality of chromosome was found in 5 out of 7 patients in this study. *PDGFRB* fusions result in the synthesis of constitutively activated tyrosine kinase fusion proteins, usually associated with continuous cell proliferation.²¹ Expression of *PDGFRB* fusions resulted in cytokine-independent proliferation and activation of phosphorylated STAT5.⁵ Cell lines and human leukemic cells expressing *PDGFRB* fusions were sensitive in vitro to dasatinib.⁵ Several signalling cascades, including the Ras/mitogen-activated protein kinase, phosphatidylinositol 3'-kinase and phospholipase- γ pathways, are key downstream mediators of *PDGFRB* signalling.⁶ Haematopoietic neoplasms with *PDGFRB* fusions are very sensitive to tyrosine kinase inhibitors (TKIs).²²

To date, 12 fusion partners of *PDGFRB* have been reported in adult B-cell acute lymphoblastic leukemia,^{21,23–26} with *EBF1–PDGFRB* being the most common.⁷ *EBF1–PDGFRB* fusion accounts for 0.5% of B-cell precursor ALL and 2.7% of the B-other subtype.⁷ The *EBF1* (*EBF1*) gene located at chromosome 5q33, is a nuclear transcription factor required for normal B-lineage specification, commitment, and development.²⁷ *EBF1–PDGFRB* fusion results in loss of *EBF1* function, multimerization and autophosphorylation of the fusion protein, activation of STAT5 signaling, and gain of IL-7-independent cell proliferation.²⁷ Deregulation and loss of *EBF1* function is critically dependent on the nuclear export activity of the TM domain of *PDGFRB*.²⁷ *EBF1–PDGFRB* synergizes with loss of *IKAROS* function in a fully penetrant B-ALL in vivo.²⁷ In this study, fusion of *EBF1–PDGFRB* was confirmed in 4 of the 7 patients. Schwab et al.⁷ reported the results of 15 cases of pediatric ALL patients with positive *EBF1–PDGFRB*, with more females than males (11/15). In this study, there was a predominance of males (3/4), heterogeneity of disease between adults and children may need to be studied to confirm this phenomenon.

In this study, two novel fusion partners of *PDGFRB* were identified: *SMIM3* and *TERF2*. In *SMIM3–PDGFRB* fusion, the *SMIM3* breaking site was exon 1, with no coding promoter region and no coding fusion protein, while the *PDGFRB* gene breaking site was exon 12 in the catalytic region of tyrosine kinase. Therefore, this case should not be classified as Ph-like ALL. In *TERF2–PDGFRB* fusion, exon 1–8 of *TERF2* gene is fused with exon 9–23 of *PDGFRB* gene, which loses the DNA binding domain of *TERF2* gene and retains the tyrosine kinase domain of *PDGFRB* gene, which is expected to be involved in the proliferation and cell cycle differentiation of leukemia cells. We are studying and verifying the related functions of *TERF2–PDGFRB* fusion gene.

Hiroto Inaba and Charles G. Mullighan reported that the CR rate was approximately 98% in pediatric patients.²⁸ However, the CR rate at the end of induction was only 57.14% in this group. The recurrence rate (28.57% vs. 46.67%) of patients in this group were lower than literature reports,⁷ suggesting that intensive chemotherapy combined with other treatment methods (target therapy and CAR-T) may benefit the patients in this group. Case 3 with TP53 mutation was classified as high-risk but achieved early deep remission after receiving hyper-CVAD A regimen, which may support this assumption. Most of all, 6 of 7 cases in our group received allo-HSCT, which was still a curative therapeutic option for adults ALL patients with *PDGFRB*. For patients received targeted therapy (Case 1, 2 and 5), case 1 achieved CR soon after administering the imatinib, however, MRD remained at 0.001 level for a long time even after CART therapy. Case 2 relapsed rapidly in 1.5 months after dasatinib administration. In case 5, the time-point of CR and CR_{MRD-} was 61 and 139 days; even if CR was achieved after induction therapy, MRD remained positive and then turned negative after CAR-T therapy. As same as adult Ph + ALL, consisting of a TKI-based induction/consolidation^{29,30} may be the suitable treatment for patients with *PDGFRB* fusion. It suggested that the targeted monotherapy is still inadequate for patients with *PDGFRB* fusion. Intensive therapy combined with CAR-T or TKI is needed to achieve deep remission for these patients. In our results, 75% (3/4) and 100% (6/6) of patients maintain MRD negative after CAR-T and Haplo-HSCT. It seem to be that sequential allo-HSCT after deep remission is expected to improve the prognosis of such patients, and we highly recommend the allo-HSCT as the consolidation if possible. Future studies in vitro and on large patients are very necessary to confirm this perspective, and this result may contribute to establish the current standard treatment paradigm for *PDGFRB* fusion in adult B-cell ALL.

Conclusion

Our results suggested that intensive therapy combined with CAR-T or TKI is needed to achieve deep remission, and sequential allo-HSCT may improve the prognosis of these patients.

Abbreviations

B-cell acute lymphoblastic leukemia (B-ALL), platelet-derived growth factor receptor B (*PDGFRB*), tyrosine kinase inhibitor (TKI), chimeric antigen receptor T - cell (CAR-T), haploid hematopoietic stem cell transplantation (Haplo-HSCT), minimal residual disease (MRD), Philadelphia-like (Ph-like), Philadelphia chromosome-positive (Ph+), Allogeneic hematopoietic stem cell transplantation (allo-HSCT), Philadelphia chromosome-negative (Ph-), Polymerase Chain Reaction (PCR), fluorescence in situ hybridization (FISH) and RNA sequencing (RNA seq), IVP (Idarubicin, Vincristine and Prednisone), Hyper-CVAD A, minimal residual disease (MRD), methotrexate (MTX) and cytarabine (Ara-C), semustine, cytarabine, busulfan, and cyclophosphamide (BuCy), umbilical cord blood (UCB), graft-versus-host disease (GvHD), Anti-Thymocyte Globulin (ATG), Complete remission (CR), partial remission (PR), Overall response rate (ORR), CR without MRD (CRMRD-), CR with MRD (CRMRD+), multiparametric flow cytometry (MFC), Cytokine Release Syndrome (CRS), acute GVHD (aGVHD) and chronic GVHD (cGVHD), white blood cell (WBC)

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional the First Affiliated Hospital of Soochow University. The patients consented to participate.

Consent for publication

Written informed consent for research and publication from the patients was obtained.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

Hui-ying Qiu and Su-ning Chen designed and supervised the study. Guo-fa Xu, Xie-bing Bao and Li-min Liu analysed data, wrote the manuscript and prepared the Figs; Man Wang and Jun-dan Xie performed experiments and measurements on samples; Zhi-bo Zhang and Zhao Zeng collected and provided the samples and contributed to manuscript preparation; De-Pei Wu contributed to study design and manuscript preparation.

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Figures

Figure 1

Clinical outcomes of adult B-ALL with PDGFRB fusion

Figure 2

EFS and OS adult of B-ALL with PDGFRB fusion