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618.ACUTE LYMPHOBLASTIC LEUKEMIAS: BIOMARKERS, MOLECULAR MARKERS AND MINIMAL RESIDUAL DISEASE IN DIAGNOSIS AND PROGNOSIS

Picalm::MLLT10 can Identify a New Subgroup of Acute Leukemias of Ambiguous Lineage with Unique Extramedullary Disease and Treatment Response

Haimin Sun[1], *Yongmei Zhu*[2], *Jianfeng Li, PhD*[3], *Lingling Zhao*[1], *Guang Yang*[1], *Zeying Yan*[1], *Ying Wang*[1], *Zhiyin Liu*[1], *Ran An*[1], *Sujiang Zhang, MD*[1]

[1] Shanghai Jiao Tong University School of Medicine Ruijin Hospital, Shanghai, China
[2] Shanghai Institute of Hematology, State Key Laboratory of Medical Genomics, National Research Center for Translational Medicine at Shanghai, Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, Shanghai, China
[3] National Research Center for Translational Research at Shanghai, Shanghai Institute of Hematology, Ruijin Hospital, Shanghai JiaoTong University School of Medicine (SJTUSM), Shanghai, China

Background: Mixed-phenotype acute leukemias (MPAL), which is included in acute leukemias of ambiguous lineage (ALAL), can be classified as four different subtypes based on recurring genetic alterations including *BCR::ABL*, *KMT2A* and *ZNF384* gene rearrangement as well as *BCL11B* activation. The 2022 WHO classification has already mentioned *PICALM::MLLT10* fusions are also enriched in MPAL but need more data. In 2022 ELN classification, *PICALM::MLLT10* was identified as acute myeloid leukemia (AML) with other rare recurring translocations but not ALAL. In addition, there is no separate classification for *PICALM::MLLT10* in the new ICC classification. Therefore, it is still confused whether *PICALM::MLLT10* corresponds to AML or acute lymphoblastic leukemia (ALL) or ALAL.
Methods: Fourteen *PICALM::MLLT10* positive patients of 390 AL patients (14/390, 3.6%) were identified by RNA sequencing (RNA-seq) in our center from 2020-2022, including 8 female and 6 male, with a median age of 33 years (16-50 years). These patients were newly diagnosed AL according to bone marrow morphology and immunology including 5 ALAL, 5 T-ALL [4 early T-cell precursor ALL (ETP-ALL), 1 cortical T-ALL], 2 AML, 1 B-ALL with aberrant expression of myeloid antigen, and 1 B/T MPAL.
Results: The mean white blood cell counts of these patients was 8.25×10^{9}/L ($2.34\text{-}51\times10^{9}$/L) and platelet counts was 168.5×10^{12}/L ($39\text{-}429\times10^{12}$/L) individually. It should be mentioned that extramedullary disease (EMD) was found in 7 cases (7/14), including mediastinum, tonsil, and skin. In terms of immunotyping, CD7 was identified in all patients (14/14) and CD33 in 71.4% (10/14) patients. The major concurrence mutations were *PHF6* mutation (8/14), *JAK3* mutation (5/14), and *SUZ12* mutation (4/14). Characteristic cytogenetic abnormality t(10;11)(p12.3;q14.2) was only found in three cases (3/14) (Table 1).
The *PICALM* breakpoints are mainly concentrated in exon 17 (n=6) and exon 19 (n=8). Exon 4 (n=8), exon 6 (n=2), exon 9 (n=2) and exon 10 (n=2) are the most commonbreakpointsof *MLLT10*. To our knowledge, this is the first report about the breakpoints and fusion gene forms of *PICALM::MLLT10*.
For initial treatment, these patients individually received standard ALL induction chemotherapy (VDPCP, vincristine, idarubicin, pegaspargase, cyclophosphamide, prednisone) and AML induction chemotherapy (3+7 IA regimen including idarubicin, cytarabine). The initial complete remission (CR) rate was only 35.7% (5/14), and 9 patients showing no remission (NR). These NR patients subsequently received salvage chemotherapy. It is worth mentioning that 6 of them received combined chemotherapy regimen including low doses of cytarabine (LDAC), granulocyte colony-stimulating factor (G-CSF) and anthracyclines such as aclarubicin or idarubicin or homoharringtonine (CAG or IAG or HAG), and 2 of 6 patients also further received combination therapy with venetoclax (CAG or IAG +VEN). Finally, 5 of them dramatically achieved CR (5/6). In the other 3 patients, 1 patient who was failure to initial Hyper-CVAD A/B regimen also dramatically achieved CR after the more Hyper-CVAD A regimen combined with venetoclax, and 1 patient achieved CR while another still NR with both receiving CLAG (cladribine, cytarabine, G-CSF) regimen. Subsequently 11 patients (9 CR, 2 with refractory disease) received allogenic hematopoietic stem cell transplantation (allo-HSCT), and all the CR patients survived well after HSCT (follow up 3-24 months, median 15 months) without relapse, while 2 NR patients died soon after transplantation because of severe complications (Table 2).
Conclusions: Our data suggested *PICALM::MLLT10* positive AL should be more appropriately recognized as an independent ALAL entity and may benefit from LDAC, G-CSF and anthracyclines combination chemotherapy as well as venetoclax. Se-

quential HSCT after chemotherapy combined with venetoclax may further improve long-term survival in AL patients with CR even MRD positive.

Disclosures No relevant conflicts of interest to declare.

Table 1. Characteristics of *PICALM::MLLT10* positive AL patients

N	G/A	WBC/ HB/PLT (×10⁹/L)	EMD	FAB/ Blast (%)	Immunophenotype	Gene mutation	Karyotype
1	M/ 44	8.73/ 128/ 133	/	AL/ 94	ALAL	SETD2, IKZF1, EED, SUZ12	86-96,XXYY,add(1p)x2, del(2q)x2, del(9q)x2, +M5~M12[cp5]
2	M/ 40	24.1/ 151/ 429	Y	ALL/ 83.7	ETP-ALL	NOTCH1, JAK3, PHF6, FAT1	44-46,XY,add(1p36), del(11q21)[cp5] /46,XY[5]
3	F/ 34	6.6/ 133/ 270	Y	AL/ 38	ALAL	EZH2, ETV6, KRAS, RUNX1, KDM6A	46, XX[20]
4	F/ 32	33/ 93/ 121	/	AL/ 93.5	ALAL	SF3B1, SETD2, ARID5B, ASXL1, PHF6	46-49,XY,del(9q31)x(10,11)(p12;q14),add (12p13),-17,+19,+M1~M2[cp6]/46,XY[4]
5	M/ 30	15.7/ 148/ 60	Y	ALL/ 71	Cortical T-ALL	NOTCH1, WT1, SUZ12, FAT1	46, XY[20]
6	M/ 34	5.69/ 152/ 330	Y	ALL/ 48	ETP-ALL	SUZ12, JAK3, PHF6, NOTCH1	46,XY,t(10,11)(p12,q14)[1] /46,XY[23]
7	F/ 28	36/ 111/ 231	/	ALL/ 70	B/T	FLT3-TKD, FBXW7, ARID1B, NF1, ASXL1, U2AF1, BCOR, PHF6	47-55,XXX,+1,+6,+7,+9, +15, +18, +21[cp4]/ 46,XX[12]
8	M/ 16	2.34/ 69/ 234	/	ALL/ 60.5	ALAL	KRAS, U2AF1, PHF6	45-48,XY,t(10,11)(p12;q14) [2]/46,XY[8]
9	M/ 50	7/ 139/ 173	/	M1/ 92	AML	SF3B1, WT1, SUZ12, ASXL3, JAK3, PHF6	46,XY,del(11)(q13q23)[20]
10	F/ 34	18.89/ 99/ 159	Y	AL /85	ALAL	PHF6, ASXL2, ETV6	45-46,del(5)(q13q21), del(11q21),del (13q21)-[6]/ 46,XX[14]
11	F/ 27	2.73/ 96/ 152	/	M5/ 55.6	AML	NRAS, ARID1A, SRPT2	46,XX[20]
12	M/ 31	51/ 165/ 164	Y	ALL/ 89.2	B-ALL	WT1, JAK3, PDGFRB, IL7R, BRCA2	43-49,XY,add(1p36),+3,+8, +18 [cp11]
13	M/ 32	4.31/ 157/ 270	Y	LBL/ 15	ETP-ALL	JAK3, CSMD1	46,XY[20]
14	F/ 36	7.78/ 86/ 39	/	ALL /77.5	ETP-ALL	NRAS, PHF6, RUNX1, JAK1, ARID1B	84~89,XXXX[cp3]/46,XX [4]

G/A, Gender/Age, Y, Yes; EMD, Extramedullary disease, LBL, Lymphoblastic lymphoma

Table 2. Clinical treatment and outcome of *PICALM::MLLT10* positive AL patients

N	Immunophenotype	Induction	Response	Reinduction	Response	Status before HSCT	HSCT	Outcome, OS (m)
1	ALAL	IA	NR	CLAG	NR	NR	Y	Die, 3
2	ETP-ALL	VDPCP	NR	CAG+VEN	CR	CR, MRD+	Y	Live, 15
3	ALAL	VDPCP	NR	CAG	CR	/	N	Die, 10
4	ALAL	IA	NR	CLAG	CR	CR, MRD+	Y	Live, 29
5	Cortical T-ALL	VDPCP	CR	/	/	CR, MRD-	Y	Live, 28
6	ETP-ALL	VDPCP	CR	/	/	CR, MRD+	Y	Live, 28
7	B/T	VDPCP	NR	CVAD, Gil, Blincyto	NR	NR	Y	Die, 10
8	ALAL	IA+VP	NR	CAG	CR	CR	Y	Live, 21
9	AML	IA	NR	HAG	CR	/	N	Die, 12
10	ALAL	IA+VP	NR	IAG+VEN	CR	/	N	Live, 7
11	AML	IA	CR	/	/	CR	Y	Live, 22
12	B-ALL	VDPCP	CR	/	/	CR, MRD+	Y	Live, 15
13	ETP-ALL	CVAD/MA	NR	CVAD +VEN	CR	CR	Y	Live, 12
14	ETP-ALL	VDPCP	CR	/	/	CR, MRD-	Y	Live, 8

IA, idarubicin and cytarabine; VDPCP, vincristine, idarubicin, cyclophosphamide, pegaspargase and prednisone; CVAD/MA, hyper-cyclophosphamide, vincristine, doxorubicin and dexamethasone alternating with methotrexate/cytarabine; VEN, venetoclax; CLAG, cladribine, high-dose cytarabine and G-CSF; CAG, LDAC, aclarubicin and G-CSF; HAG, LDAC, homoharringtonine and G-CSF; IAG, LDAC, idarubicin and G-CSF; Gil, Gilteritinib; Blincyto, Blinatumomab; MRD, measurable residual disease.

Figure 1

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