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Philadelphia positive T-acute lymphoblastic leukemia: a Mayo Clinic series

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Conflict of Interest

The authors declare no conflicts of interest related to this work.

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The Philadelphia (Ph) chromosome is the hallmark cytogenetic aberration in chronic myeloid leukemia (CML), including both chronic phase (CP) and blast phase (BP), as well as in Ph chromosome-positive (Ph+) acute lymphoblastic leukemia (ALL) (1, 2). Nearly all cases of Ph+ ALL are of B-lymphoblastic lineage. Rare cases of T-lineage disease have nevertheless been reported, either as *de novo* Ph+ T-ALL or as T-lymphoid BP of CML (3-12). The largest series by investigators from MD Anderson Cancer Center included 5 patients with Ph+ T-cell lymphoid CML-BP and 2 patients with *de novo* Ph+ T-ALL (13).

Here, we report our experience with Ph+ ALL and CML-BP of T-lymphoid lineage at the Mayo Clinic Comprehensive Cancer Center. The study was deemed exempt from review by the Mayo Clinic institutional review board. We identified 5 patients with Ph+ T-lymphoid leukemia, including 4 with de novo Ph+ T-ALL and one with T-lymphoid BP of antecedent CML, diagnosed between 2014 and 2022. Median age was 73 years (range, 49–74); 4 patients were male, and 4 were Non-Hispanic White **(Table 1)**. All presented with lymphadenopathy, 4 had bone marrow (BM) T-lymphoblastic leukemic involvement, and none had CNS involvement at diagnosis. The frequency of Philadelphia chromosome-positive T-lineage disease was 6% (4/66) of all adult T-ALL diagnoses during the 2014–2022 period, underscoring the rarity of this entity.

Below, we summarize the clinical course of each patient from initial diagnosis through subsequent treatment and outcomes. Detailed patient, disease, treatment, and outcome characteristics are summarized in **Table 1** and **Figure 1**. Representative immunophenotypic and cytogenetic findings from Patient 4 are shown in **Figure 2**. The immunophenotypes of blast populations in all five patients are summarized in **Supplementary Figure 1**.

Patient 1. A previously healthy 49-year-old man initially presented with 40-pound weight loss, drenching night sweats, and marked splenomegaly measuring 27 cm craniocaudally, evolving over 6 months. Evaluation at an outside hospital demonstrated CML-CP with <5% marrow blasts and t(9;22), producing a p210 *BCR::ABL1* transcript. One week later, while awaiting TKI approval and receiving hydroxyurea for cytoreduction, he developed progressive

bulky cervical lymphadenopathy with white blood cell (WBC) count of 185×10⁹/L. Imaging revealed extensive cervical and thoracic adenopathy, with the largest right scalene conglomerate measuring 5×3×2 cm. Excisional biopsy of a left cervical lymph node demonstrated T-lymphoblastic lymphoma with a high proliferative index. Fluorescence in-situ hybridization (FISH) confirmed *BCR::ABL1* fusion in 94% of nuclei resulting in p210 transcripts, consistent with T-lymphoblastic crisis of CML. He underwent emergent cytoreduction with leukapheresis and hydroxyurea, followed by hyper-CVAD plus dasatinib, achieved complete remission (CR), and proceeded to matched related donor allogeneic stem cell transplantation (SCT). He died 5.3 years after diagnosis from cardiopulmonary complications of chronic GVHD with his disease in complete molecular response (CMR).

Patient 2. A 49-year-old man with chronic obstructive pulmonary disease, obstructive sleep apnea, morbid obesity, and dilated cardiomyopathy presented with several weeks of progressive neck swelling and several days of worsening respiratory status. Imaging revealed diffuse cervical, thoracic, abdominal, and pelvic lymphadenopathy with marked hepatosplenomegaly. Peripheral blood demonstrated a WBC count of 127×10⁹/L with 69% blasts. Subsequent BM evaluation showed T-ALL with 78% blasts. BM FISH demonstrated *BCR::ABL1* fusion in 80% of nuclei, supporting a diagnosis of *de novo* Ph+ T-ALL. He underwent cytoreduction with leukapheresis, hydroxyurea, and prednisone, but died seven days after diagnosis from progressive disease in the setting of substantial comorbidity and inability to receive intensive induction therapy.

Patient 3. A 74-year-old man with hypertension and coronary artery disease status post four coronary stents presented with fatigue, weakness, night sweats, and splenomegaly measuring 18 cm. Peripheral blood showed leukocytosis (22.6×10^9/L), 12% circulating blasts expressing CD2, CD5, and CD7, mild basophilia, and thrombocytopenia. BM evaluation confirmed T-lymphoblastic leukemia/lymphoma with 76% blasts. He received 1 cycle of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone) at an outside institution before

cytogenetic and FISH results became available, achieving an initial hematologic response but developing prolonged pancytopenia. Subsequent studies demonstrated t(9;22) with additional copies of the Ph-chromosome and *BCR::ABL1* fusion in 86% of nuclei resulting in a p210 transcript. Despite the absence of a known prior history of CML, the relative basophilia and occasional small monolobated megakaryocytes raised the suspicion of possible antecedent CML. He was treated with prednisone followed by dasatinib 140 mg daily and achieved morphologic CR after 2 months of therapy; however, residual disease persisted, with *BCR::ABL1* fusion still detectable in 9% of nuclei by FISH. He therefore received 7 cycles of mini-hyperCVD (hyperfractionated cyclophosphamide, vincristine, and dexamethasone) plus dasatinib, ultimately achieving a complete cytogenetic response (CcyR) at 7 months. Dasatinib maintenance was later complicated by pleural effusions, prompting transition to high-dose imatinib 600 mg daily. He achieved MMR 6.4 years after diagnosis and remained alive in MMR at 8.6 years.

Patient 4. A 74-year-old man with type 2 diabetes mellitus, rheumatoid arthritis, atrial fibrillation status post ablation and pacemaker placement on chronic anticoagulation, and heart failure with preserved ejection fraction presented with persistent fatigue and one month of right cervical lymphadenopathy. ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography/computed tomography (PET/CT) revealed extensive cervical, axillary, mediastinal, retroperitoneal, bilateral iliac, and inguinal lymphadenopathy, with the largest node in the right axilla measuring 3.3 cm and demonstrating a maximum standardized uptake value (SUV) of 5.0. Excisional biopsy of the right axillary node demonstrated TdT-positive T-lymphoblastic lymphoma. Peripheral blood and BM studies confirmed T-ALL, with 50% peripheral blood blasts (WBC, 29×10^9/L) and 30% BM blasts. Cytogenetics identified t(9;22) and a subclone with an 11q deletion and monosomy 21. FISH demonstrated *BCR::ABL1* fusion in 48% of nuclei, resulting in p190 transcripts. He received dexamethasone for cytoreduction followed by one cycle of vincristine plus dasatinib, achieving CCyR but died 2.2 months after diagnosis from treatment-related complications, including pulmonary edema and functional decline.

Patient 5. A 73-year-old woman with type 2 diabetes mellitus, hypertension, gastroesophageal reflux disease, obstructive sleep apnea, obesity, peripheral neuropathy, and arthritis presented with weight loss, fatigue, drenching night sweats, and cervical lymphadenopathy. She was diagnosed with T-ALL with 2% peripheral blood blasts (WBC, 11×10^9/L) and 57% BM blasts with a high proliferative index. Biopsy of a right cervical lymph node confirmed T-lymphoblastic lymphomary. Cytogenetics identified t(9;22) with trisomy 19, and FISH demonstrated *BCR::ABL1* fusion in 48% of nuclei, resulting in p210 transcripts. She received induction therapy with dasatinib, vincristine, and dexamethasone and achieved CR, after which she transitioned to maintenance therapy with 6-mercaptopurine and dasatinib. Her subsequent course was complicated by bilateral pleural effusions and acute decompensated heart failure 4 months after diagnosis, necessitating temporary interruption of TKI therapy. She died 1.8 years after diagnosis with her T-ALL in CCyR.

In summary, extramedullary involvement was common (80%), and immunophenotypes were consistent with immature T-lineage disease: cCD3 (100%) with CD2 (100%), CD5 (100%), CD7 (100%), and TdT (100%). No case demonstrated an early T-precursor phenotype. Aberrant myeloid antigen expression was limited (CD13 in 2, CD33 in 1). None of the cases satisfied the immunophenotypic criteria for Ph+ mixed-phenotype acute leukemia or acute leukemia of ambiguous lineage. In patients with T-lymphoblastic leukemic involvement, BM blasts ranged from 30% to 78%. Four of 5 patients had cytogenetic abnormalities beyond the Philadelphia chromosome. Of note, among the 4 patients receiving treatment, the single patient (Patient 4) harboring a p190 transcript had the shortest survival. Treatment strategies varied and included hyperCVAD+dasatinib (n=1), mini-hyperCVD+dasatinib (n=1), vincristine+dexamethasone+dasatinib (n=2), and best supportive care (n=1). All 4 treated patients achieved CR, and none developed overt hematologic, cytogenetic, or extramedullary relapse. Two patients died within 3 months of diagnosis due to disease progression or treatment-related complications. One patient underwent allogeneic SCT in CR, and he remained in CMR but died

5.3 years later from chronic GVHD-related complications. One patient remained alive at last follow-up in MMR on imatinib at 8.6 years. Median overall survival was 21 months (range 0.3–103).

Ph+ T-lineage lymphoblastic leukemias/lymphomas are exceedingly rare and, in our series, occurred predominantly in older adults with consistent nodal involvement at presentation. None of the patients had prior TKI exposure, arguing against a therapy-related lineage switch. These cases also underscore the diagnostic difficulty of distinguishing *de novo* Ph+ T-ALL from T-lymphoid CML-BP when antecedent CP is not clearly documented.

Outcomes were heterogeneous and appeared to depend not only on disease biology but also on baseline comorbidity burden and treatment tolerability. Nevertheless, meaningful and occasionally durable remissions were achievable in patients able to receive leukemia-directed therapy, including long-term survival beyond 8 years in one patient and sustained disease control after allogeneic SCT in another. By contrast, early mortality occurred in patients with substantial frailty, comorbidity, or inability to tolerate intensive treatment.

Our study has important limitations, including the lack of comprehensive next-generation sequencing (NGS), absence of flow cytometric- or NGS-based measurable residual disease assessment, and lack of IKZF1plus evaluation. Targeted *ABL1* kinase domain mutation testing was performed in Patients 3 and 4 and was negative. Nonetheless, the cases were well annotated from the clinical, cytogenetic, and morphologic standpoints, and were followed longitudinally by qRT-PCR, with key molecular milestones shown in **Figure 1**, allowing meaningful descriptive analysis despite these constraints. Collaborative multi-institutional efforts are needed to refine classification, better define the biology of these neoplasms, and optimize treatment approaches. Our findings support consideration of routine baseline testing for *BCR::ABL1* in patients presenting with T-ALL, especially when clinical or morphologic features such as splenomegaly, basophilia, or extensive extramedullary disease raise concern for an underlying Ph+ process.

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Table 1. Clinical, Immunophenotypic, Molecular, Treatment, and Outcome Characteristics of Patients with Philadelphia Chromosome-Positive T-Cell Acute Lymphoblastic Leukemia

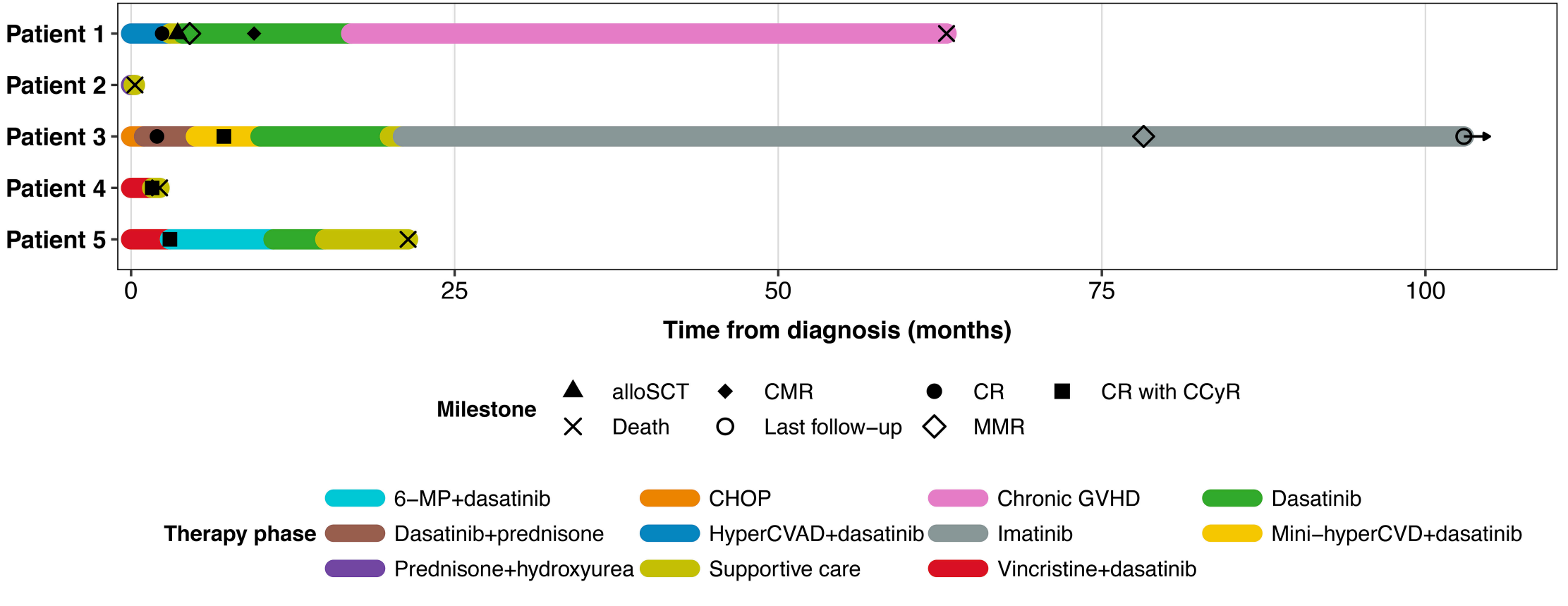
Case Number	Age at diagnosis, years	Sex (M/F)	Race/Ethnicity	CML-BP or *de novo* ALL	T-LL or T-ALL	*bcr::abl1* transcript type	ECOG PS	BMI (kg/m^2)	Lymphadenopathy	Splenomegaly	Mediastinal mass	CNS involvement	LDH (U/L)	WBC (×10^9/L)	Hemoglobin (g/dL)	Platelets (×10^9/L)	PB blasts (%)	BM blasts (%)	TdT expression	Karyotype	Prior TKI therapy	Induction chemotherapy	TKI used	CR after induction	Allogeneic HSCT	Survival status	OS (months)	Disease status at last follow-up
1	49	M	Non-Hispanic White	CML-BP	T-LL	e14-a2 p210	0	23	Y	Y	N	N	485	185	9.2	501	0	2	dim	46,XY,t(9;22)(q34;q11.2)[13]/47,XY,idem,+8[6]/48,XY,idem,+8,-13,+19,+21[1]	N	Y	Dasatinib	Y	Y	Deceased	63	CMR
2	49	M	Non-Hispanic White	*de novo* ALL	T-ALL	Not done	3	63	Y	Y	N	N	999	127	9.6	100	66	79	+	46,XY,t(9;22)(q34;q11.2)[8]/46,XY[12]	N	N	None	N/A	N	Deceased	0.3	PD
3	74	M	Non-Hispanic White	*de novo* ALL	T-ALL	e14-a2 p210	0	27	Y	Y	N	N	261	23	11.4	70	10	76	+	46,XY,t(9;22)(q34;q11.2)[2]/47,sl,+der(22)t(9;22) [7]/47,XY,der(9)t(9;22)(q34;q11.2),ider(22)(q11.2)t(9;22)[cp9]/46, XY[2]	N	Y	Dasatinib → imatinib	Y	N	Alive	103	MMR
4	74	M	Non-Hispanic White	*de novo* ALL	T-ALL	e1-a2 p190	0	26	Y	Y	N	N	203	29	11.4	80	50	30	partial/variable	46,XY,t(9;22)(q34;q11.2)[1]/45,XY,t(9;22)(q34;q11.2),del (11)(q13q21),-21[6]/46,XY[13]	N	Y	Dasatinib	Y	N	Deceased	2.2	CR with CCyR
5	73	F	African American	*de novo* ALL	T-ALL	e13/e14-a2 p210	3	65	Y	N	N	N	374	11	11.8	155	2	57	+	47,XX,t(9;22)(q34;q11.2),+19[4]/46,XX[16]	N	Y	Dasatinib	Y	N	Deceased	21.4	CR with CCyR

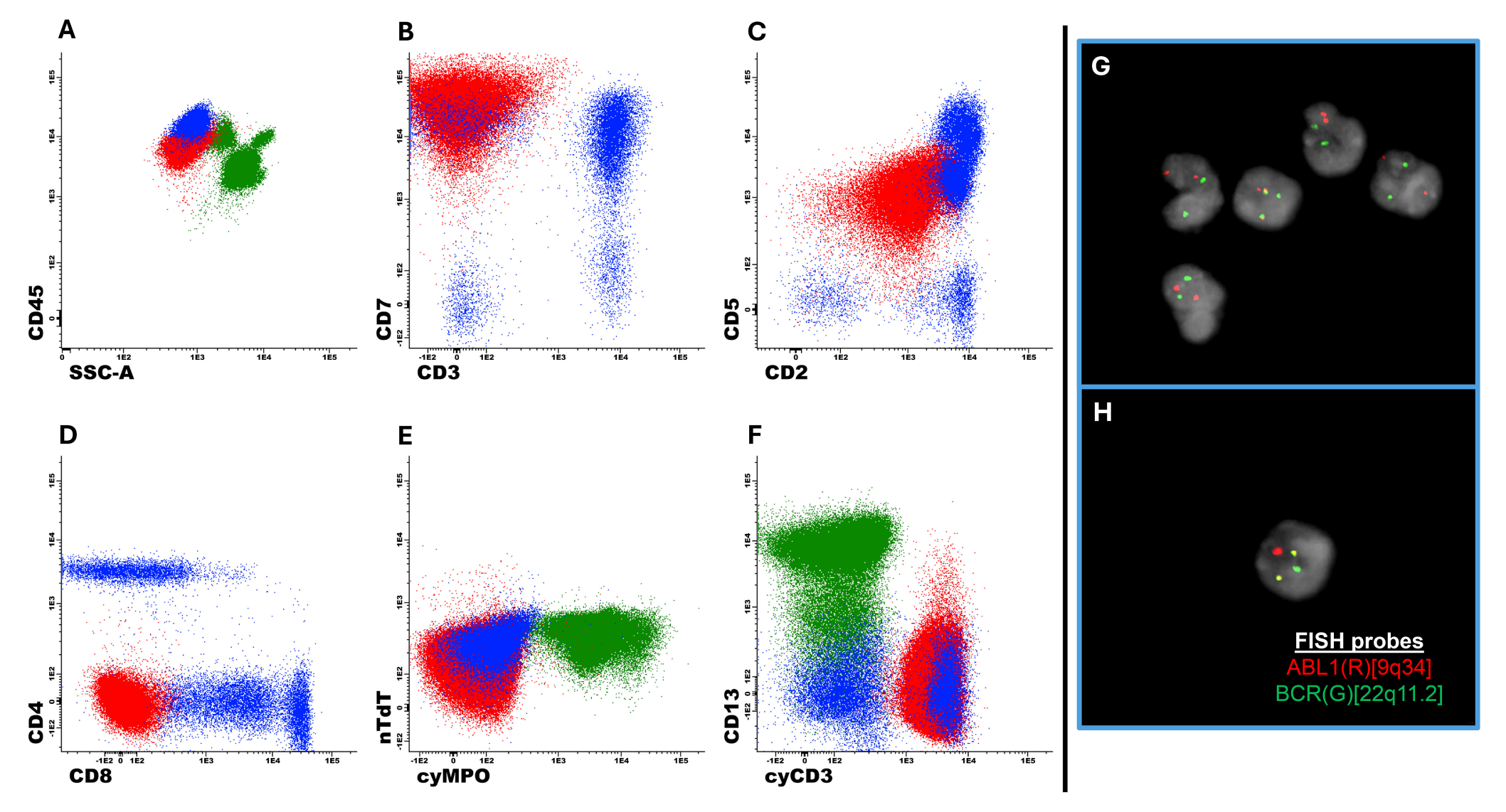
Abbreviations: BM, bone marrow; BMI, body mass index; CCyR, complete cytogenetic response; CML-BP, chronic myeloid leukemia in blast phase; CMR, complete molecular response; CR, complete remission; CNS, central nervous system; ECOG PS, Eastern Cooperative Oncology Group performance status; F, female; M, male; LDH, lactate dehydrogenase (upper limit of normal: 222 U/L); MMR, major molecular response; OS, overall survival; PD, progressive disease; T-ALL, T-cell acute lymphoblastic leukemia; T-LL, T-cell lymphoblastic lymphoma; TKI, tyrosine kinase inhibitor; WBC, white blood cells.

FIGURES

Figure 1. Swimmer plot of treatment course and key clinical milestones in patients with Philadelphia chromosome-positive T-ALL. hyperCVAD, hyperfractionated cyclophosphamide + vincristine + doxorubicin + dexamethasone; hyperCVD, hyperfractionated cyclophosphamide + vincristine + dexamethasone; CHOP, cyclophosphamide + doxorubicin + vincristine + prednisone; 6-MP, 6-mercaptopurine; GVHD, chronic graft-versus-host disease; CR, complete remission; CCyR, complete cytogenetic response; alloSCT, allogeneic stem cell transplant; CMR, complete molecular response; MMR, major molecular response.

Figure 2. Flow cytometric and cytogenetic findings in Patient 4. (A–F) Flow cytometric analysis of the bone marrow demonstrates an abnormal blast population (red), with lymphocytes shown in blue and myeloid/monocytic cells shown in green. (G, H) Fluorescence in situ hybridization (FISH) performed on the same bone marrow specimen demonstrates *BCR::ABL1* fusion.


Patient 1
Patient 2
Patient 3
Patient 4
Patient 5
0
25
50
75
100
Time from diagnosis (months)
Milestone
alloSCT
CMR
CR
CR with CCyR
Death
Last follow−up
MMR
Therapy phase
6−MP+dasatinib
CHOP
Chronic GVHD
Dasatinib
Dasatinib+prednisone
HyperCVAD+dasatinib
Imatinib
Mini−hyperCVD+dasatinib
Prednisone+hydroxyurea
Supportive care
Vincristine+dasatinib


A
CD45
SSC-A
B
CD7
CD3
C
CD5
CD2
D
CD4
CD8
E
nTdT
cyMPO
F
CD13
cyCD3
G
H
FISH probes
ABL1(R)[9q34]
BCR(G)[22q11.2]

SUPPLEMENTARY FIGURES

Figure S1. Immunophenotypic profile of blast populations in all five patients, as determined by flow cytometry and/or immunohistochemistry. Green indicates positive expression, red indicates negative expression, yellow indicates dim or weak expression, and white indicates not assessed.

Marker	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
CD1a	+	–	+	–	–
CD2	+	+	+	+	+
CD3	+	–	+	–	+
cCD3	+	+	+	+	+
CD4	–	–	–	–	–
CD5	+	+	+	+	+
CD7	+	+	+	+	+
CD8	–	–	–	–	–
CD10	–	–	+	–	–
CD13	+	+	–	–	–
CD19	–	–	–	–	–
CD20	–		–	–	–
CD22	–	–	–		
cCD22	–	–		–	
CD33	+	–	–	–	–
CD34	–	–	+	–	+
CD38		+			
CD45	+	dim	+	+	+
CD56		–		–	+
cCD79a	–	–		–	
CD117		–	–	weak	–
HLA-DR		–			–
cMPO	–	–	–	–	–
nTdT	dim	+	+	partial / variable	+

Legend

+	Positive
–	Negative
dim/weak	Dim/weak
	Not assessed