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Clinical characteristics of Philadelphia positive T-cell lymphoid leukemias – (de novo and blast phase CML)

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The Philadelphia chromosome (Ph+) is a hallmark of CML and is also present in a subset of patients with acute lymphoblastic leukemia (ALL). Patients presenting with clinical features of T cell lineage leukemia and Ph chromosome can suggest either a T-ALL or lymphoid blast phase of CML with T-lineage.[1–4] Lymphoid blast phase (CML-BP) and Ph+ ALL almost always affect B cell lineage and very rarely involve T cell lineage or present with mixed phenotype[5]. It is unclear as to how the presence of Ph chromosome or BCR-ABL protein is associated in regulating the differentiation or the lineage switch of leukemic stem cells. Presence of Ph+ is documented in precursor B cells from CML patients in chronic phase.[6]

In this report, we present the clinical characteristics of the rare subset of patients with Ph+ ALL or CML-BP with T-cell lymphoid phenotype. We reviewed the institutional database for all patients with blast phase CML (n=498) and *de novo* T-ALL (n=150) diagnosed since 07/1997. All clinical characteristics at the time of the diagnosis of BP or Ph+ ALL and treatment course were collected. Seven patients with Ph+ T-cell lymphoid leukemia were identified.

Among the total of 498 CML-BP patients, 5 patients had T-cell lymphoid CML-BP (0.01%); in addition 2 patients with *de novo* Ph+ T-ALL were identified among 150 patients with T-ALL seen during the same time period (1.3%). Median age of the seven patients was 57 years (range 31–72 years); 71% were male. Among patients with CML-BP, all were in BP at the time they were referred to our institution (one had progressed from an initial diagnosis in CP, 1 from accelerated phase, and 3 were in BP at initial diagnosis). Only 2 patients with CML-BP received prior TKI therapy; the 2 patients with T-ALL were previously untreated at the time of referral. Immunophenotype included 2 cortical, 3 early T-cell and 2 early T-cell

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Authorship Contributions

P.J., and J.C. Contributed to the study design, data collection, wrote the paper and analyzed results. R. K-S., H.K., K.P. and S.P., analyzed molecular data, H.K., F.R., E.J., G.B., G.M.G., S.O.B., and J.C. contributed patient samples.

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precursor; 2 patients were negative and one was dim positive for TdT *(summarized in* Table-1). Extramedullary disease at initial presentation was seen in all patients [2 with lymphadenopathy alone, 2 with mediastinal involvement (one also with lymphadenopathy and the other with splenomegaly and lymphadenopathy), 2 with pleural effusion (1 with lymphadenopathy and another with splenomegaly) and 1 patient with splenomegaly alone]. None had central nervous system (CNS) involvement at initial presentation, but one patient developed CNS involvement at first relapse. One patient had variant Ph+ and 2 had complex karyotype. Three patients had lymphoblastic lymphoma and 4 patients had T-ALL. Five patients died (3 from disease progression, one from complications of stem cell transplantation (SCT), and one from intestinal obstruction and sepsis) and 2 are alive (25 and 49 months from BP diagnosis). The median survival for all patients was 13 months (range 1–49 months).

Five patients received hyper-CVAD based therapy as an induction regimen: 3 of them received hyper-CVAD alone – one achieved CR then underwent a SCT but died due to complications of SCT, another achieved PR and was given imatinib followed by dasatinib which he did not tolerate; he was subsequently lost to follow up; and one patient had no response. The other 2 patients received hyper-CVAD with dasatinib – one achieved PR, then underwent allo-SCT and achieved CR but later had a CNS relapse and progressed; the other patient developed nodal progression 9 months after achieving CR with HCVAD-dasatinib which was later found to represent metastatic prostate cancer in the lymph nodes with no T-ALL recurrence and is currently on dasatinib with major molecular response. Two patients never received any TKI (tyrosine kinase inhibitor) therapy and progressed on chemotherapy alone. Two patients received nelarabine as first salvage – one as a single agent (no response) and another with dasatinib (with PR).

According to the literature, <50 cases of T-lineage acute leukemia with Ph chromosome have been reported, mainly as an anecdotal case report.[7,8] These included a mixture of patients with T-ALL and/or lymphoid blast phase CML. Extramedullary involvement with lymph nodes, mediastinum, liver and spleen was frequent[1] and outcomes were dismal. T-cell lymphoid CML-BP has been described in the past.[5] A diagnosis of prior CML was not observed in all patients with T-cell lymphoid CML-BP but majority of these patients had a prior CML. It is difficult to differentiate between T-cell lymphoid CML-BP vs a denovo T-ALL, however features which favor the T-cell lymphoid CML-BP over denovo T-ALL are history of prior CML, presence of non-e1a2 BCR-ABL transcripts, adult age group, extramedullary disease, absence of lymphoblastic leukemia in the bone marrow and excellent response to therapy with second generation TKI combined with intensive chemotherapy HCVAD.

In our experience, Ph+ T-cell lymphoid leukemias are extremely rare and have clinical features similar to those of *de novo* T-ALL. Pathogenesis of T cell lineage differentiation of leukemic stem cells in adults with Ph+ leukemias is unclear. Outcomes of these patients are generally poor, however induction with a combination of HCVAD and second generation TKI's may achieve prolonged remission in some patients.

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Table 1

Summary of patients with Ph+ T-cell lymphoid leukemia's (CML-BP) and denovo T-ALL

Patient ID	**1**	**2**	**3**	**4**	**5**	**6**	**7**
CML-BP or De-Novo T-ALL	CML	CML	CML	CML	CML	T-ALL	T-ALL
Ph+ T cell lymphoid leukemia subtype	Cortical	Early T precursor	Cortical	Early-T cell	Early T precursor	Early-T cell	Early-T cell
Prior TKI (Y/N) and Type of TKI	N	Y, Imatinib, Dasatinib	N	Y, Dasatinib	N	N	N
Survival Status	Dead	Dead	Alive	Alive	Dead	Dead	Dead
Overall survival after diagnosis of CML-BP/ T-ALL (months)	4	13	25	49	1	14	0.1
Gender (M/F)	M	M	F	M	M	F	M
Ethnicity	Hispanic	Hispanic	White	Black	White	White	Hispanic
Age (years)	32	42	64	63	57	31	72
BCR-ABL Transcript Type	e14a2	e13a2	e1a2	e13a2 & e14a2	e13a2	e1a2	e1a2
Hemoglobin (g/dL)	9.6	8.8	16	10	9.7	9.5	8.6
WBC Count (K/uL)	267	6.1	17	213	60	6.5	39
Platelet Count (K/uL)	343	15	191	204	35	13,000	26
Peripheral Blood Blast %	3	0	0	3	5	ND	81
Serum LDH	367	455	583	1060	2052	ND	887
Initial BM Blast (%)	1	15	4	0	21	28	74
T-LL/T-ALL (Y/N)	T-LL	T-ALL	T-LL	T-LL	T-ALL	T-ALL	T-ALL
ABL Mutations and Type	Not done	A337P	Not done	None	Not done	Not done	Not done
TdT	Negative	Positive	Positive	Positive	Negative	Positive	Dim
Status at last follow up	Progressive disease; Died	Progressive disease; Died	Not in remission, lost to follow up	PCyR and MMR	Progressive disease/Comorbidities; Died	Died with complication of SCT	Died of intestinal obstruction, sepsis