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The many faces (and phenotypes) of BCR::ABL1-driven acute leukemia

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In the current issue of *Haematologica*, Burgess et al. report a Mayo Clinic series of five patients with Philadelphia chromosome-positive (Ph+) T-acute lymphoblastic leukemia (T-ALL), including four cases classified as *de novo* Ph+ T-ALL and one patient with T-lymphoid leukemia in blast phase of chronic myeloid leukemia (CML) (1). Although small, this carefully annotated series adds to a limited body of prior reports describing the uncommon occurrence of BCR::ABL1 in T-ALL. Together with earlier case reports and small series (2-3), this study illustrates the clinical and phenotypic diversity of BCR::ABL1-driven acute leukemias.

The initial description by Nowell and Hungerford of a recurrent “minute chromosome" in chronic granulocytic leukemia, followed by Janet Rowley’s recognition of the reciprocal t(9;22) translocation and the subsequent identification of the BCR::ABL1 fusion gene, established one of the earliest models of cancer as a genetically defined disease (4). This discovery ultimately led to the development of imatinib, a therapeutic milestone that transformed CML from a life-threatening myeloid neoplasm into a disease compatible with near-normal life expectancy for many patients receiving tyrosine kinase inhibition (TKI).

BCR::ABL1 is now also recognized as a somatic driver lesion across several types of acute leukemias (**Figure 1**). The most frequent and well-established of these is Ph+ B-cell precursor (BCP)-ALL, a genetically defined subtype of BCP-ALL that can present as lymphoid-restricted disease (ALL-L), or as BCP-ALL with multilineage involvement (ALL-M; 'CML-like') (5). The phenotypic plasticity of BCR::ABL1 driven acute leukemia is further highlighted in the diagnostic category of Mixed-Phenotype Acute Leukemia (MPAL), where Ph+ disease defines a genetic subgroup enriched for B/Myeloid phenotype and comprises up to 15-20% of adult MPAL patients (6). More recently, AML with BCR::ABL1 fusion was recognized in both WHO-HAEM5 (6) and the ICC (7) diagnostic frameworks as a rare genetically defined AML entity (<1% of adult *de-novo* AML cases), although both classifications retain a ≥20% blast requirement to limit overlap with CML presenting in accelerated or myeloid blast phase.

In contrast to these formally recognized entities, BCR::ABL1-positive T-ALL represents a rare and ill-defined disease phenotype in the spectrum of BCR::ABL1-driven acute leukemias. Unlike BCP-ALL, MPAL, and AML, BCR::ABL1-positivity does not currently define a formal genetic subgroup of T-ALL (8).

From a mechanistic perspective, the phenotypic heterogeneity of BCR::ABL1-positive leukemias is determined by several factors, including the developmental stage of the cell of origin at the time of leukemic transformation, acquisition of additional somatic genetic alterations, and

interactions with the bone marrow microenvironment. Transcriptomic profiling of patients with Ph+ BCP-ALL identified three molecular subtypes corresponding to distinct stages of B-cell developmental arrest, each characterized by unique patterns of cooperating genetic alterations. Among these classes, the most immature expressed stem and myeloid programs and was associated with greater lineage promiscuity and poor clinical outcomes (9). In an analysis of 1855 patients with Ph+ leukemia, the e1a2 fusion transcript (corresponding to p190 protein) was strongly associated with lymphoid leukemia, whereas the e13a2 and e14a2 transcripts (encoding the p210 isoform) were more frequent in multilineage or CML-like disease. Among patients with p210-positive CML, lymphoid blast transformation was associated with BCR::ABL1 amplification or kinase-domain mutations, whereas myeloid transformation more often accompanied AML-related abnormalities, including inv(3)/MECOM and t(3;21)/RUNX1::MECOM (10). The bone marrow microenvironment also appears to contribute to lineage determination. Reynaud *et al.* identified IL-6 as a leukemia-induced paracrine signal that directs multipotent progenitors toward myeloid differentiation in a murine model of CML (11). Zhang *et al.* demonstrated that BCR::ABL1 remodels the marrow niche through altered CXCL12 and cytokine expression, thereby preferentially supporting leukemic stem cells expansion (12).

Distinguishing between blast-phase CML and *de-novo* Ph+ acute leukemia remains a major diagnostic challenge with important therapeutic implications regardless of the expressed phenotype. Clinical and pathological features suggestive of CML blast phase include a prior history of leukocytosis, splenomegaly, marked basophilia, expression of the p210 BCR::ABL1 isoform, CML-like bone marrow morphology, characteristic patterns of cooperating genetic alterations, and demonstration of multi-lineage involvement of BCR::ABL1. However, no single feature is sufficiently sensitive or specific to establish the diagnosis in isolation. One important principle is that regardless of the specific ontogeny underlying the development of Ph+ acute leukemia, the incorporation of TKI should remain the cornerstone of any therapeutic approach chosen.

The series by Burgess et al. identified Ph+ T-lineage disease in 4 of 66 (6%) adult T-ALL diagnoses during the study period, emphasizing the rarity of this phenotype while raising the possibility that it may be under-diagnosed when BCR::ABL1 testing is not routinely performed in all cases of T-ALL. Clinically, these cases appeared enriched for extramedullary disease: lymphadenopathy was universal, splenomegaly was frequent, with no patient demonstrating CNS involvement at diagnosis. Immunophenotypically, the cases were consistent with immature T-lineage immunophenotype but none met criteria for ETP-ALL or MPAL.

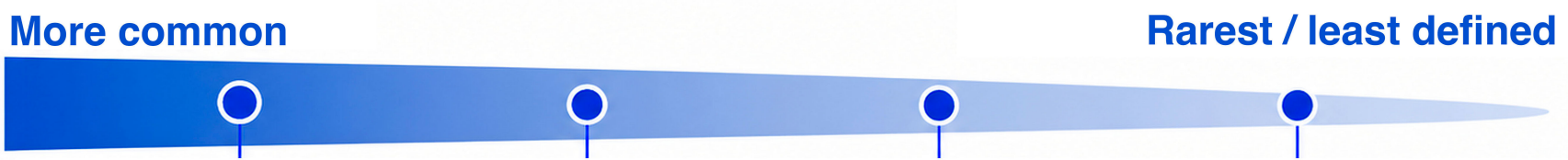
From a therapeutic perspective, the Mayo experience highlights both the promise and the limitations of current treatment approaches. All treated patients received TKI-containing regimens with high remission rates, supporting the clinical relevance of identifying BCR::ABL1 in T-lineage disease. Yet overall outcomes were shaped not only by initial response to therapy, but also by age, comorbidity burden, treatment tolerance, and transplant-related toxicity.

The routine implementation of comprehensive genomic profiling platforms, including optical genome mapping (OGM), RNA sequencing, and multiplex PCR-based fusion assays in newly diagnosed ALL is likely to improve detection of Ph+ T-ALL and more accurately define its true incidence in the future. Further characterizing the genomic landscape of these leukemias, and defining the role of TKI-based therapy and MRD-guided clinical management in this patient subset are essential for improving patient management, and may potentially inform future classification of this genetic subgroup.

References:

(1) Burgess AR, Ali H, Zarka J, et al. Philadelphia positive T-acute lymphoblastic leukemia: a Mayo Clinic series. Haematologica. xxx
(2) Raanani P, Trakhtenbrot L, Rechavi G, et al. Philadelphia-chromosome-positive T-lymphoblastic leukemia: acute leukemia or chronic myelogenous leukemia blastic crisis. Acta Haematol. 2005;113(3):181-189.
(3) Jain P, Kantarjian H, Jabbour E, et al. Clinical characteristics of Philadelphia positive T-cell lymphoid leukemias - (De novo and blast phase CML). Am J Hematol. 2017;92(1):E3-E4.
(4) Deininger M, Buchdunger E, Druker BJ. The development of imatinib as a therapeutic agent for chronic myeloid leukemia. Blood. 2005;105(7):2640-2653.
(5) Duffield AS, Mullighan CG, Borowitz MJ. International Consensus Classification of acute lymphoblastic leukemia/lymphoma. Virchows Arch. 2023;482(1):11-26.
(6) Khoury JD, Solary E, Abla O, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: myeloid and histiocytic/dendritic neoplasms. Leukemia. 2022;36(7):1703-1719.
(7) Arber DA, Orazi A, Hasserjian RP, et al. International consensus classification of myeloid neoplasms and acute leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
(8) Alaggio R, Amador C, Anagnostopoulos I, et al. The 5th edition of the World Health Organization Classification of Haematolymphoid Tumours: lymphoid neoplasms. Leukemia. 2022;36(7):1720-1748.
(9) Kim JC, Chan-Seng-Yue M, Ge S, et al. Transcriptomic classes of BCR-ABL1 lymphoblastic leukemia. Nat Genet. 2023;55(7):1186-1197.
(10) Jones D, Luthra R, Cortes J, et al. BCR-ABL fusion transcript types and levels and their interaction with secondary genetic changes in determining the phenotype of Philadelphia chromosome-positive leukemias. Blood. 2008;112(13):5190-5192.
(11) Reynaud D, Pietras E, Barry-Holson K, et al. IL-6 controls leukemic multipotent progenitor cell fate and contributes to chronic myelogenous leukemia development. Cancer Cell. 2011;20(5):661-673.
(12) Zhang B, Ho YW, Huang Q, et al. Altered microenvironmental regulation of leukemic and normal stem cells in chronic myelogenous leukemia. Cancer Cell. 2012;21(4):577-592.

Legend to Figure 1. Phenotypic spectrum of *de novo* BCR::ABL1-positive acute leukemias. Frequencies are derived from different denominators and should be interpreted as a relative rarity spectrum rather than directly comparable population incidences. Cases of CML in blast phase are excluded.



BCR::ABL1-positive phenotype	Approximate frequency	Immunophenotypic and genetic characteristics	Therapeutic approach
B-lymphoblastic leukaemia/lymphoma with *BCR::ABL1* fusion	~20–30% of adult ALL; frequency increases with age, reaching ~40% in adults >50 years	B-lineage lymphoblasts; frequent CD13/CD33 expression; p190 predominant; recurrent IKZF1/PAX5/ CDKN2A/B alterations.	TKI-based therapy; combination with chemotherapy and/or immunotherapy; MRD-directed decisions
MPAL with *BCR::ABL1* fusion	Accounts for 15–20% of MPAL cases.	Meets MPAL criteria, usually B/myeloid; p190/p210 variable; additional cytogenetic abnormalities in a minority.	TKI-based therapy; combination with chemotherapy and/or immunotherapy; MRD-directed decisions
AML with *BCR::ABL1* fusion	Accounts for < 0.5% of AML cases.	Myeloid blasts, often CD34/HLA-DR/CD13/CD33/ CD117; usually p210; *RUNX1* mutations frequent.	TKI-based therapy; combination with chemotherapy (e.g. “7+3”, FLAG)
***BCR::ABL1*-positive T-ALL/T-LBL**	Mostly case reports and small series; 4 cases among 66 adult T-ALL diagnoses in the current study	Immature T-lineage phenotype; not MPAL; co-mutational landscape poorly defined.	TKI-based therapy; Optimal approach unknown