Seminars in Diagnostic Pathology (2011) 28, 124-134

ELSEVIER

Seminars in
Diagnostic
Pathology

Pathobiology of acute lymphoblastic leukemia

Stefania Paolini, MD, Anna Gazzola, BS, MS, Elena Sabattini, MD, Francesco Bacci, MD, Stefano Pileri, MD, Pier Paolo Piccaluga, MD, PhD

From the Molecular Pathology Laboratory, Hematology and Hematopathology Sections, Department of Haematology and Oncology "L. and A. Seràgnoli," S. Orsola-Malpighi Hospital, University of Bologna, Bologna, Italy.

KEYWORDS
Acute lymphoblastic leukemia;
WHO classification;
BCR/ABL1;
NOTCH1;
Targeted therapy

In the present review, the authors described the pathobiological features of B- and T-ALL, which appear to be quite heterogeneous with regard to molecular pathogenesis. The last edition of the World Health Organization Classification considered this aspect by defining many entities based on genetic findings. This approach is not only important for prognostic stratification, but also in the near future will surely represent the basis for the definition of patient-specific therapeutic approaches. A striking example is Ph^+ acute lymphoblastic leukemia (ALL), which until the advent of tyrosine kinase inhibitors (TKI) has been regarded as the most aggressive ALL. The use of imatinib, dasatinib, and possibly more recent inhibitors has dramatically changed the clinical scenario, offering new opportunities to patients, especially the elderly. Similarly, the use of FLT3 inhibitors in mixed lineage leukemia–positive cases, γ-secretase inhibitors in T-ALL, novel TKI, and monoclonal antibodies may represent a successful approach in the future.

Background

Acute lymphoblastic leukemia (ALL) is the most common childhood cancer worldwide, occurring in 1/50,000 people per year, 70% of whom are younger 19 years old. The World Health Organization (WHO) currently recognizes 3 main ALL subgroups: B-ALL not otherwise specified, B-ALL with recurrent genomic abnormalities, and T-ALL (Table 1). In addition, ALLs are further classified based on the degree of differentiation of the B-lineage lymphoblasts according to immunophenotype.[1–3] Such a distinction has clinical and genetic correlates, and leukemia-associated phenotypes can be used for minimal residual disease detection.

The prognosis of ALL is relatively good in children, with up to 80% of patients reported cured. Adult patients have a less favorable prognosis, although the most recent intensified chemotherapy regimes led to up to 40%-50% long-term complete remissions.[4,5] Thus, novel approaches are warranted. In this regard, one the most prominent themes of contemporary research on hematological malignancies is to understand the consequences of the most frequent genetic lesions in terms of their effects on cell proliferation, differentiation, and survival and then to develop selectively targeted treatments against the altered gene products (or affected pathways) to which the leukemic clones have become addicted.[6,7] Interestingly, such a translational approach offered new therapeutic opportunities in ALL, revealing specific targets in certain subgroups, such as *BCR-ABL1*$^+$ (treated with combinations containing tyrosine kinase inhibitors [TKI]) or T-ALL (treated with nelarabine or with γ-secretase inhibitors [GSI]; see below).

In this article, the authors review the most updated concepts on ALL pathobiology and provide examples of genetic-driven targeted therapy for selected ALL subgroups.

Address reprint requests and correspondence: Pier Paolo Piccaluga, MD, PhD, Molecular Pathology Laboratory, Hematopathology Section, Department of Haematology and Oncology "L. and A. Seràgnoli," S. Orsola-Malpighi Hospital, University of Bologna, Via Massarenti, 9, 40138 Bologna, Italy.
E-mail address: pierpaolo.piccaluga@unibo.it.

0740-2570/$ -see front matter
doi:10.1053/j.semdp.2011.02.008

Table 1 Classification of precursor lymphoid neoplasms according to the World Health Organization

B lymphoblastic leukemia/lymphoma, not otherwise specified
B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities
B lymphoblastic leukemia/lymphoma with t(9:22)(q34;q11.2); *BCR-ABL1*
B lymphoblastic leukemia/lymphoma with t(v;11q23); *MLL* rearranged
B lymphoblastic leukemia/lymphoma with t(12;21)(p13;q22); TEL-AML1 (ETV6-RUNX1)
B lymphoblastic leukemia/lymphoma with hyperdiploidy
B lymphoblastic leukemia/lymphoma with hypodiploidy (hypodiploid ALL)
B lymphoblastic leukemia/lymphoma with t(5;14)(q31;q32)/*IL3-IGHV@*
B lymphoblastic leukemia/lymphoma with t(1;19)(q23;p13.3); *E2A-PBX1 (TCF3-PBX1)*
T lymphoblastic leukemia/lymphoma

Cellular derivation and diagnosis

ALL cells usually present with clonal rearrangements of their immunoglobulin or T-cell receptor (TCR) genes and express antigen-receptor molecules with immunophenotypes that largely recapitulate those of immature lymphoid progenitor cells within the early developmental stages of normal T and B lymphocytes.[6,8-10] Accordingly, ALL is currently thought to stem from bone marrow progenitor cells, committed to differentiate in the T-cell or B-cell lineage, because of various founding genetic lesions that affect their capacity for unlimited self-renewal and lead to precise stage-specific developmental arrest.[6,8,9] In some instances, the first molecular event of the multistep process might arise in a hemopoietic stem cell possessing multilineage developmental capacity.[6,11]

According to the WHO, immunophenotyping of leukemic lymphoblasts by flow cytometry or immunohistochemistry on bone marrow trephine biopsy (in case of dry tap) is essential to establish the correct diagnosis and define cell lineage.[1-3] Although ALL can be readily subclassified according to the many steps of normal B-cell and T-cell differentiation, using current protocols the only findings with therapeutic importance are the distinction of B-ALL from mature B-cell leukemias (ie, Burkitt's leukemia in the WHO Classification) and T-cell phenotypes.[6,12,13] Myeloid-associated antigen expression can be detected but is not associated with prognostic implications. By contrast, the identification of leukemia-associated phenotypes can be useful for detection and monitoring of minimal residual disease.[6,14] The latter is also commonly studied by molecular techniques, including clonality tests for immunoglobulin heavy chain (*IGHV@*) and TCR (*TRG@/TRB@*) genes and tumor-specific rearrangement analysis using tightly standardized quantitative polymerase chain reaction.[15]

In addition, conventional metaphase cytogenetics, sometimes integrated by reverse transcription polymerase chain reaction and fluorescence in situ hybridization, is an integral part of the initial diagnostic workup for ALL, used to detect specific genomic imbalances provided with prognostic or therapeutic relevance (see below).[6,12,13]

Pathobiology

The etiology of ALL at present is mostly unknown. In fact, only a minority of cases (<5%) are associated with exposure to carcinogens (including ionizing radiation, chemicals, or specific chemotherapeutic drugs) or with inherited, predisposing genetic syndromes (including Down's syndrome, Bloom's syndrome, ataxia-telangiectasia, and Nijmegen breakage syndrome).[6] In addition, some factors have been proposed to confer an increased risk for this disease (including exposure to pesticides, solvents, or power-frequency magnetic fields),[6,16,17] but these data are inconsistent. In addition, the combination of environmental and genetic factors has been related to the development of prenatal ALL.[6] In this regard, several studies have been performed with a focus on possible maternal exposure to various substances and the genetic variability in xenobiotic metabolism, DNA repair pathways, and cell-cycle checkpoint functions. A few data exist to support a possible causal role for single nucleotide polymorphisms in genes encoding for cytochrome P450, NAD(P)H quinine oxidoreductase, glutathione *S*-transferases, methylenetetahydrofolate reductase, thymidylate synthase, serine hydroxymethyltransferase, and cell-cycle inhibitors.[6,18-23] Intriguingly, dietary, medical, and environmental exposure to substances that inhibit topoisomerases and the reduced ability of fetuses or their mothers to detoxify such agents were associated with development of infant leukemia with mixed lineage leukemia (*MLL*) gene rearrangement,[6,12,24] a genetic abnormality frequently encountered in secondary leukemias that arose after exposure to topoisomerase II inhibitors.[6,25]

In contrast to etiology, the pathogenesis of many ALL subtypes has been extensively studied recently. In particular, although the exact mechanisms leading to malignant transformation are unknown, possible founding lesions as well as several pathways contributing to the leukemic phenotype have been identified. According to the WHO Classification, chromosomal translocations that activate specific genes are a defining characteristic of B-ALL, allowing the distinction of the so-called B-ALL with recurrent genomic abnormalities (Table 1).[2,8,9] Gene expression profile studies have substantiated the idea that specific chromosomal translocations identify unique subtypes of the disease.[6,26-30]

In the following sections, the main recurrent cytogenetic abnormalities (Table 2) will be discussed.

Structural abnormalities

Structural abnormalities (ie, chromosomal translocations) represent the most common recurrent genetic lesions