Lymphoblastic Leukemia / Lymphoma

Definition

Lymphoblastic leukemia/lymphoma is a systemic neoplasm of precursor B or T lymphocytes (lymphoblasts) that primarily involves the bone marrow and blood as acute lymphoblastic leukemia (ALL) but occasionally presents first in extramedullary sites. The designation of lymphoblastic lymphoma (LL) is used when the neoplasm is confined to lymph nodes or other extramedullary sites with no or minimal blood and marrow involvement.

Incidence

The incidence of lymphoblastic leukemia/lymphoma in the United States was approximately 1.8/100,000 population/year in 2011. About 4/100,000 individuals less than 15 years of age and 8/100,000 between ages 1 and 5 years were afflicted, making ALL the most common type of cancer in children. Approximately 80% of cases of acute leukemia in children and 20% in adults are lymphoblastic. The male to female ratio is about 1.16 to 1.
Classification

A revised WHO Classification of lymphoblastic neoplasms is expected in 2017 and is shown below:

**Proposed WHO Classification of Lymphoblastic Neoplasms--2017**

B lymphoblastic leukemia/lymphoma, NOS

B lymphoblastic leukemia/lymphoma (B LL/L) with recurrent genetic abnormalities

- B LL/L with t(9;22)(q34.1;q11.2); **BCR-ABL1**
- B LL/L with t(v;11q23.3); **KMT2A/MLL** rearranged
- B LL/L with t(12;21)(p13.2;q22.1); **ETV6-RUNX1/TEL-AML1**
- B LL/L with hyperdiploidy
- BLL/L with hypodiploidy
  - Near haploid
  - Low hypodiploid

- B LL/L with t(5;14)(q31.1;q32.1); **IGH/IL3**
- B LL/L with (1;19)(q23;p13.3); **TCF3-PBX1/E2A-PBX1**
- B LL/L **BCR-ABL1**-like (provisional)
- B LL/L with iAMP21 (provisional)

T lymphoblastic leukemia/lymphoma

- Early T-cell precursor LL/L (provisional)

Natural killer cell leukemia/lymphoma (provisional)

B lymphoblastic leukemia/lymphoma is the most common of the two major immunophenotypic groups of the WHO Classification, accounting for about 85% of cases in children and 75% in adults. T lymphoblastic leukemia/lymphoma, comprises about 15% of cases in children and 25% in adults. B lymphoblastic leukemia/lymphoma is further divided into two subgroups based on genetic findings: B lymphoblastic leukemia/lymphoma not otherwise specified and B lymphoblastic leukemia/lymphoma with recurrent genetic abnormalities (9 categories, 2 of them provisional). T lymphoblastic neoplasms consist of the major group and one provisional sub-category, early T-cell lymphoblastic leukemia/lymphoma.
Variant Morphologic Features and Presentations in LL/L

The variant morphologic features and presentations described below are most frequently found in B LL/L but may also be encountered in or T LL/L.

**LL/L with cytoplasmic granules.** Azurophilic granules are observed in the cytoplasm of lymphoblasts in 4.5% to 7% of cases of LL/L. The granules vary in size but are often larger than the azurophilic granules in myeloblasts. Some stain weakly and appear slightly pink or orange in Romanowsky stained smears. Occasionally the granules appear to coalesce or are aggregated in one area of the cytoplasm. The granules are negative for myeloperoxidase but may be faintly PAS positive and rarely stain for Sudan black B.

Cytoplasmic granules are found in both B LL/L and T LL/L. There have been no consistent cytogenetic associations but granules appear to be found more often in B LL/L in children with Down’s Syndrome and cases with a t(9;22). This may explain why granulated lymphoblasts have been associated with a less favorable prognosis in children with B LL/L in some studies. The presence of granulated lymphoblasts is mainly important because of the potential for confusion with myeloblasts.

**Marked vacuolation.** Vacuoles are commonly found in lymphoblasts in LL/L and may correspond to glycogen deposits, dilated organelles or lipid inclusions. They may lead to confusion in diagnosis when particularly abundant and may mimic the vacuoles found in Burkitt lymphoma cells.

**Mature appearing blast morphology.** The lymphoblasts in occasional cases of L/LL have more condensed chromatin and other features that suggest a mature stage of maturation. In children this generally causes little difficulty in diagnosis but in adults ALL with these features must be distinguished from lymphoproliferative disorders of small mature B lymphocytes, e.g., chronic lymphocytic leukemia, mantle cell lymphoma, marginal zone lymphoma. This can be readily accomplished by immunophenotyping in nearly all cases.

**Aplastic presentation of LL/L.** Rarely, patients with LL/L present with pancytopenia and a hypoplastic bone marrow. This hypocellular phase is typically followed by partial marrow recovery and later by overt leukemia within weeks or a few months. In contrast to the hypocellular myelodysplastic syndromes that may precede AML, dysplastic changes are not observed in the hypoplastic phase preceding LL/L.
There are no reported distinctive morphologic, immunophenotypic or cytogenetic characteristics associated with the overt leukemic phase.

**Bone marrow necrosis.** Patients with LL/L may present with partial or extensive bone marrow necrosis. The finding always suggests a neoplasm; in children the first consideration is LL/L but Burkitt lymphoma and metastatic small cell neoplasms may also present with extensive necrosis. When the entire marrow specimen is necrotic a definitive diagnosis may be difficult. A repeat marrow biopsy from the other iliac crest is helpful in some cases but if marrow necrosis is extensive it may be necessary to wait several days to obtain a diagnostic biopsy if there are not obvious lymphoblasts in the blood.

**Relapse of lymphoblastic leukemia.** In most cases the morphology of the lymphoblasts at relapse is similar to those in the diagnostic marrow. In a minority of patients morphologic evolution occurs, usually to larger blasts with more prominent nucleoli. Immunophenotypic and karyotypic evolution may also be observed at relapse. A summary of changes in lymphoblasts at relapse is shown in.

Bone marrow relapse is most frequent (~75%) but isolated extramedullary relapse occurs in a minority of patients. In marrow the blast count is low in early relapse with scattered or small clusters of lymphoblasts. Occasionally the pattern is focal and recognition of relapse is particularly difficult. Immunohistochemical stains can be helpful in distinguishing recurrent LL/L from normal B cell precursors (hematogones) and flow cytometry and molecular methods are highly sensitive for detecting small numbers of residual/recurrent lymphoblasts.

Central nervous system (CNS) involvement with LL/L occurs in about 5% of cases at diagnosis and is the most common site of extramedullary relapse (~20% of relapses). In males the testicles are the second most common site of extramedullary relapse (~5% of relapses). Other sites include skin, eye and lymph nodes. In some cases with extramedullary relapse occult disease is detected in the marrow.

CNS involvement is usually diagnosed by spinal fluid examination (CSF). Cytospin preparations are preferred. Blasts may be abundant and the diagnosis obvious or only occasional ones may be found. When CSF involvement is minimal the lymphoblasts may not be detected by morphologic examination of cytospins or the interpretation may be ambiguous because of the difficulty in distinguishing lymphoblasts from reactive cells in some cases. Immunostains for CD10, CD34 or TdT can aid in the
assessment. Multiparameter flow cytometry is highly sensitive and can enhance the detection of neoplastic cells in CSF when an adequate amount of fluid is available.

**Therapy Related Acute Myeloid Leukemia (AML).** Therapy related AML has been reported in 0.27% to 6% of patients treated for LL/L. It appears to be more common in T LL/L than B LL/L. This most likely reflects differences in treatment regimen. The AML is presumed to result from effects of chemotherapy on myeloid stem cells. Topoisomerase II inhibitor drugs, usually an epipodophyllotoxin, have most often been implicated. Typically the AML presents from one to four years after the initiation of therapy. Most of the topoisomerase II inhibitor related leukemias have been monocytic or myelomonocytic but several other categories of AML including megakaryoblastic have been reported. A rearrangement of chromosome 11 at band q23, the site of the MLL gene, is generally found in the AML clone. AML following treatment for LL/L carries a poor prognosis. Although many patients initially respond to induction chemotherapy for AML, they nearly always relapse unless allogeneic stem cell transplantation is performed.

**The following discussion of immunophenotype and genetics emphasizes the findings in B LL/L. The distinctive features of T LL/L follow in a later discussion on features unique to T LL/L.**

**Immunophenotype**

Immunophenotyping is essential at diagnosis in all cases of lymphoblastic leukemia/lymphoma (LL/L). Appropriate immunophenotyping can differentiate ALL from AML in nearly all cases and distinguish B LL/L and T LL/L. In addition, treatment and prognostic groups are determined partly by immunophenotype. The profile of antigen expression on the leukemic blasts also serves as an important fingerprint for later assessment for minimal residual disease. The lineage of acute leukemias is determined by the pattern of antigen expression by the neoplastic blasts. For leukemias multiparametric flow cytometry is the preferred method for determining immunophenotype, however, in some situations immunohistochemistry is used to compliment flow cytometry and may be essential when only biopsy sections are available.

It is important to use panels of antibodies that assess several antigens
associated with each of the major hematopoietic lineages. Most of the lineage-associated antibodies used for immunophenotyping are relatively specific but not lineage-restricted. Also, acute leukemias of a particular lineage have notoriously heterogeneous immunophenotypes. Limited antibody panels, particularly ones that include only antibodies to a single lineage, can result in misinterpretation because of aberrant or biphenotypic antigen expression.

The major immunophenotypic categories of precursor lymphoid neoplasms are B LL/L and T LL/L. Subtypes of each are defined by patterns of intra-lineage antigen expression. The lymphoblasts in B L/L/L express various combinations of the B lymphocyte associated antigens CD19, CD22, CD79a, CD24, CD10, and CD9 and several lineage non-specific antigens including CD34, TdT, HLADR, CD38 and CD45.

Approximately 98% of cases express HLADR and the pan-B-cell antigen CD19. In the diagnosis of B LL/L both are quite specific and rarely found in T LL/L but HLADR is expressed in most cases of AML and CD19 in some. CD22 is present in nearly all cases of B LL/L; it is highly sensitive and quite specific but cross-reactivity has been reported in some cases of AML and rarely in T LL/L in adults. CD79a is a cytoplasmic antigen that is also present in the vast majority of cases. Although initially thought to be specific for B LL/L in the diagnosis of acute leukemia, CD79a expression is found in some cases of AML and T LL/L. CD24 and CD9 are expressed in 90% to 95% of cases but are only relatively specific. CD10, is found in about 90% of cases of B LL/L in children but is absent in the majority of infants with B LL/L and in ~25% of adults. Up to 35% of cases of T LL/L are CD10 positive. CD20 is highly specific for B LL/L in the diagnosis of acute leukemia but is lacking in many cases. Mu immunoglobulin heavy chains (Clg) are present in the cytoplasm of the lymphoblasts in 20% to 25% of B LL/L but except in rare cases lymphoblasts lack expression of Slg. More than 90% of cases of B LL/L are TdT(+) and the progenitor cell associated antigen CD34 is found in about 75%. TdT is useful in differentiating B LL/L from lymphoproliferative disorders of mature lymphocytes, which are TdT negative, but 90% of T LL/L and 5% to 10% of AML also express TdT. Furthermore, TdT is not specifically a marker of neoplastic blasts for up to 10% positive cells, corresponding to stage 1 hematogones (normal B lymphocyte precursors) may be found in marrow from healthy individuals, especially young children. Other markers that lack lineage specificity but are commonly expressed in B LL/L include CD38, in most cases, and CD45 in about 70%. The intensity of expression of
the different antigens varies from case to case.

B LL/L can be divided into immunophenotypic subtypes based on expression of various combinations of progenitor cell and B lymphocyte associated antigens, cytoplasmic mu and surface immunoglobulin. These subtypes roughly parallel the stages of normal B lymphocyte maturation. However, most cases of B LL/L deviate from the normal stages by asynchronous and aberrant expression of antigens. Only a few cases express phenotypes that would be considered synchronous with a normal stage of differentiation. Furthermore, the clinical and prognostic significance once attributed to some of the subsets of B LL/L has largely been eclipsed by present-day therapy.

Asynchronous and Aberrant Antigen Expression. In virtually all cases of B LL/L the lymphoblasts exhibit incomplete maturation and immunophenotypic asynchrony and aberrancy that deviates from the spectrum of antigen expression typical of normal B lymphocyte stages of maturation. Over-, under-, and lack of expression of one or more B lymphocyte associated antigen is found in nearly all cases. More than half of B LL/L co-express combinations of early and late antigens not present on normal B cell precursors (asynchronous antigen expression). Some of the more common aberrancies relative to normal B lymphocyte precursors are uniform expression of TdT and CD34, negative or under-expression of CD45, CD20, HLADR and CD38, over-expression of CD10, abnormal spectrum of expression of CD22 and co-expression of CD34 and CD20. In 30% to 80% of cases one or more myeloid associated antigen is detected on the neoplastic lymphoblasts. CD15, CD13 and CD33 appear to be most common. The prognostic significance of myeloid antigen expression in LL/L is discussed in the section on Treatment and Prognosis.

Phenotypic changes at relapse. At relapse lymphoblasts express the same major immunophenotype as at diagnosis but often losses or gains of individual antigens are observed. Loss or gain of TdT, CD10, CD34 or HLADR are among the most frequently reported. Very rarely a major change in phenotype occurs from B to T ALL or to AML. These are usually examples of therapy related leukemia rather than clonal evolution.

Genetics

Cytogenetic/molecular findings are a valuable indicator of prognosis in B LL/L.
High and low risk groups are defined by cytogenetic findings and treatment determined by risk group. It is essential that cytogenetic studies be performed on pre-treatment marrow specimens in all case of L/LL.

When studied by conventional cytogenetics the lymphoblasts in 80% to 90% of cases of B LL/L have demonstrable chromosome abnormalitie. The incidence is even higher when molecular cytogenetic techniques are used to supplement conventional studies. Fluorescence in situ hybridization (FISH) can be particularly valuable when rearranged segments of chromosomes are too small to be recognized by conventional banding. FISH is also useful when specimens are too small or hypocellular for successful tissue culture.

The major recurrent cytogenetic abnormalities define categories of B LL/L in the WHO Classification. These will be proceeded by an asterisk (*) in the discussion that follows.

**Chromosome Numerical Groups in B ALL/LL**

Chromosome numerical changes are found in about 50% of children and 15% in adults with B LL/L. In children ploidy defines important prognostic groups but in adults has little effect on prognosis except in a small group of hypodiploid cases. There are five major chromosome numerical groups: hyperdiploid with more than 50, hyperdiploid with 47 to 50, diploid, hypodiploid and pseudodiploid.

*Hyperdiploidy with more than 50 chromosomes (high hyperdyploidy)* is found in 25% of children and about 5% to 14% of adults with B LL/L and correlates with a DNA index of more than 1.16. In children hyperdiploidy >50 is associated with favorable clinical features and an excellent prognosis; long term event free survival is upwards of 90%. There are prognostic variables in B LL/L with hyperdiploidy >50. Duplication of any two or three of chromosomes 4, 10, and 17 appears to impart a particularly favorable prognosis. Duplication of chromosome 18 may also have favorable prognostic significance and an extra number 5 seems to confer less good outcome. Assessment for duplication of these chromosomes can be done by interphase FISH analysis if conventional cytogenetic studies are not available.

Cases with structural changes, particularly translocations, in addition to >50 chromosomes may have a less favorable prognosis. The favorable outcome in B LL/L
with hyperdiploidy >50 appears to be related to increased sensitivity to anti-metabolite drugs.

**Hyperdiploidy with 47 to 50 chromosomes** is found in approximately 15% of cases. Structural abnormalities are present in roughly half of these, translocations in one third. There are no specific presenting clinical features associated with this group but, relative to B LL/L with hyperdiploidy >50, patients are more often older and have elevated leukocyte counts. The prognosis is considered intermediate but risk stratification treatment protocols have improved outcomes for this group.

A normal diploid number of chromosomes is found in about 10% of cases of B LL/L in children and 30% in adults. There are no specific clinical findings in this intermediate prognostic group.

**Hypodiploidy (<46 chromosomes)** is an uncommon cytogenetic abnormality comprising approximately 5% of B LL/L and is associated with a poor outcome. In adults with B LL/L hypodiploidy is the one numerical chromosome abnormality with independent prognostic value. A majority of patients with hypodiploidy have 45 chromosomes in their leukemic blasts with deletion of chromosome 20 being most common. These patients have a better outcome than patients with fewer than 45.

Hypodiploidy with fewer than 45 chromosomes has been stratified according to modal chromosome number into 4 groups:

- **Near-diploid:** 44 chromosomes
- **High-hypodiploid:** 40 to 43 chromosomes
- **Low-hypodiploid:** 33 to 39 chromosomes
- **Near-haploid:** 24 to 29 chromosomes

Patients with 44 chromosomes have a better outcome than those with fewer than 44. The most common groups with fewer than 44 chromosomes are near-haploid (~1% of cases of B LL/L) and low-hypodiploid. Both of these groups are associated with a poor prognosis. Distinctive recurring genomic alterations occur in near-haploid and low-hypodiploid B LL/L. In near-haploid cases these include alterations targeting IKZF3, RAS signaling and receptor tyrosine kinase signaling and in low-hypodiploid alterations in IKZF2, TP53 and RB1. There are no reported defining clinical, morphologic or immunophenotypic features associated with hypodiploid B LL/L.

**Pseudodiploidy** (46 chromosomes but with structural abnormalities) is found in approximately 40% of children with B LL/L and in 55% of adults. The prognostic
implications in this group depend directly on the structural abnormality. There are favorable, unfavorable and intermediate prognosis categories in this group; one of the best, t(12;21), and two of the poorest, t(9;22) and t(4;11), prognostic types are usually pseudodiploid.

**Chromosome Structural Changes in B LL/L**

Structural changes are always present in pseudodiploid B LL/L and may be found in the other numerical groups except diploid. Translocations are most important because several recurrent ones are independent indicators of prognosis.

*t(9;22)(q34.1;q11.2); BCR/ABL1, (Philadelphia(Ph1) chromosome). B LL/L arises from a reciprocal translocation involving the cytoplasmic tyrosine kinase gene ABL on chromosome 9q34.1 and the BCR (breakpoint cluster region) on chromosome 22q11.2. This translocation results in a hybrid BCR/ABL1 gene that is transcribed into a chimeric messenger RNA, which encodes a chimeric tyrosine kinase oncogene. The t(9;22) is found in the lymphoblasts of approximately 2 to 4% of children with LL/L and ~25% of adults, making it the most common structural abnormality in adults with LL/L; in patients over 50 it is found in up to 44% of cases. The karyotype of the translocation is identical to the one found in chronic myeloid leukemia (CML).

In approximately 25 to 50% of cases of t(9;22) B LL/L in adults and 10% to 20% in children the ABL gene from chromosome 9 transposes into the major breakpoint cluster region (M-bcr) resulting in a BCR/ABL1 fusion protein of 210 kD (p210\textsuperscript{BCR/ABL}), the same as that in most cases of CML. In the remaining cases the breakpoint on chromosome 22 is in the minor breakpoint cluster region (m-bcr) producing a smaller 190 kD fusion protein (p190\textsuperscript{BCR/ABL}).

Translocation (9;22) cases span the spectrum of morphology for LL/L. There are no defining cytologic features but there appears to be a higher proportion of cases with a predominance of large blasts with prominent nucleoli than for other B LL/L and cytoplasmic granules are more commonly observed. Nearly all cases of t(9;22) LL/L have a precursor B immunophenotype but there is variation in the antigen profile between cases and myeloid associated antigens are often aberrantly expressed.

Translocation (9;22) B LL/L is characterized by an older age and high presenting leukocyte counts and, in some studies, more frequent organomegaly and central nervous system (CNS) involvement. The prognosis is unfavorable in both children and
adults. Even with intensive therapy complete remission rates are significantly less than with other categories of B LL/L and long-term disease free survival rates are relatively low. Use of tyrosine kinase inhibitor drugs has improved treatment response. Patients with BCR/ABL1 B LL/L with associated deletion of IKZF1 have been shown to respond less favorably to chemotherapy, including tyrosine kinase inhibitors, than those without a IKZF1 deletion. Presently, allogeneic bone marrow transplantation in first remission offers the most realistic opportunity for improved overall survival in IKZF1 deleted BCR/ABL1 B LL/L.

*B LL/L with t(v;11q23.3);KMT2A/MLL Rearranged. Abnormalities of chromosome 11q23 are found in up to 80% of infants with B LL/L and ~10% of older children and adults. Abnormalities of 11q23 include deletions, duplications, inversions and reciprocal translocations. For the WHO classification, however, only recurrent translocations at 11q23 that involve the KMT2A/MLL gene are include. There are numerous partner genes in KMT2A/MLL translocations; the AF4 gene at 4q21 which partners in the t(4;11)(q21;q23)-AF4/KMT2A is the most frequent, occurring in about 60% of infants, 2% of other children and 3% to 6% of adults with B LL/L. The t(11;19)(q23;p13)-KMT2A/ENL and t(9;11)(p21;q23)-AF9/KMT2A, frequent in 11q23 rearrangements in AML, are less common in B LL/L.

The leukocyte count is typically markedly increased in t(4;11) B LL/L. In blood and marrow smears there are no defining cytologic features. The spectrum of cytologic findings typical of LL/L in general is also found in t(4;11) LL/L. In cases of bilineal t(4;11) leukemia both lymphoblasts and neoplastic myeloid cell, usually monoblasts and promonocytes, are observed.

The immunophenotype is characteristically that of early precursor B LL/L: CD10(-), CD24(-), TdT(+), CD34(+), CD19(+), HLADR(+). The myeloid associated antigen CD15 is present in the majority of cases and CD13 and CD33 are commonly expressed. In cases of bilineal leukemia there is an immunophenotypic mixture of lymphoblasts with the typical t(4;11) B LL/L immunophenotype and neoplastic myeloid cells expressing only myeloid antigens.

The presence of an KMT2A/MLL rearrangement is significantly associated with high-risk clinical features; age <1 year, markedly elevated leukocyte counts and a relatively high frequency of CNS involvement. The prognosis is among the worst for LL/L with a high rate of relapse and poor overall survival. Cases with deletions,
inversions or translocations of 11q23 that spare the KMT2A/MLL gene do not manifest the same adverse prognosis.

*t(1;19)(q23;p13.3), TCF3/PBX1 (E2A/PBX1) B LL/L. The t(1;19) is the most frequent translocation identified by conventional cytogenetics in children with B LL/L. It is found in 5% to 6% of patients, 25% of Clg(+), (pre-B ALL) cases and ~ 1% of Clg(-); it is slightly less common in adults. The translocation may be balanced, t(1;19)(q23;p13.3), or unbalanced, der(19)t(1;19)(q23;p13.3). In either, the breakpoint on chromosome 19 is at p13.3 within the transcription factor-encoding gene TCF3. TCF3 is fused with the PBX1 gene on chromosome 1q23 (TCF3/PBX1).

There are no distinctive morphologic findings associated with t(1;19) B LL/L but the large majority of cases exhibit typical small or intermediate sized lymphoblasts. The immunophenotype of the lymphoblasts is characterized by homogeneous expression of CD19, CD10, and CD9, absent CD34 and absent or under-expression of CD20.

High risk features have been reported in B LL/L with t(1;19) including high leukocyte counts, more frequent CNS involvement and black race. Recent studies, however, have not corroborated the high frequency of these adverse features. The unbalanced der(19) reportedly confers a better prognosis than the balanced t(1;19). There is suggestive evidence that patients with an isolated t(1;19) may have a better event free survival than those with additional chromosome abnormalities. The poor prognosis once ascribed to Clg+ B LL/, and attributed specifically to the t(1;19), appears to have been overcome by contemporary therapies. Overall survival rates now compare favorably with other types of B LL/L.

*t(12;21)(p13.2;q22.1), ETV6/RUNX1 (TEL/AML1). The t(12;21) is a cryptic translocation not found by conventional cytogenetic karyotyping because the rearranged segments are too small to be recognized. The translocation is identified by molecular techniques, e.g., FISH or PCR. The t(12;21)(p13.2;q22.1) fuses the transcriptional repressor ETV6 gene at 12p13.2 to RUNX1, the DNA-binding subunit of the RUNX1/CBFβ transcription factor complex, on chromosome 21q22.1.

The ETV6/RUNX1 fusion is found in approximately 25% of children and 3% to 4% of adults with B LL/L making it the most common translocation in childhood LL/L. In some patients t(12;21) is the only cytogenetic aberrancy and the karyotype appears normal. In others additional abnormalities are present but high-hyperdiploidy (>50 chromosomes) is virtually never observed with t(12;21). In most cases patients with
non-hyperdiploid B LL/L that lack t(9;22), t(4;11) and t(1;19) should be studied for the
ETV6/RUNX1 by FISH or PCR because of its treatment and prognostic implications.

There are no distinctive morphologic features associated with t(12;21) B LL/L and
the Immunophenotype is generally that of common B LL/L. Bright CD10 and HLADR,
lack of expression of CD9 and CD20 and increased frequency of expression of the
myeloid associated antigens CD13 and CD33 are characteristic.

Most studies suggest that t(12;21) B LL/L has an excellent prognosis. Patients
are mostly in the favorable 1 to 10 year age group (75% are 3 to 6 years) and lack high
risk factors. They respond well to conventional anti-metabolite-based therapy with
remission rates approaching 100% and excellent event free and overall survival.
However, late relapses occur with some frequency. Copy number genome alterations
have recently been shown to effect treatment response and outcome in relapsed
childhood ETV6-RUNX1 B LL/L.

*t(5;14)(q31.1;q32.1); IL-3-IgH* is a rare type of acute leukemia associated with
hypereosinophilia and comprising less than 1% of cases of B LL/L. The chromosomal
translocation joins the interleukin-3 gene (*IL-3*) at 5q31.1 with the immunoglobulin heavy
chain gene at 14q32.1 forming a fusion gene (*IL-3/IgH*) that results in excess IL-3
messenger RNA and elevated serum IL-3 levels. The excess IL-3 presumably triggers
increased production of eosinophils in the marrow.

There are no reported unique morphologic or immunophenotypic features of the
lymphoblasts that distinguish them from those in other types of B LL/L. The associated
eosinophilia is reactive and not a component of the clonal leukemic proliferation. The
immunophenotype is that of a common B LL/L with CD19 and CD10 expression.

B LL/L with t(5;14) occurs in both children and adults with a median patient age
of 14 years. Patients frequently present with symptoms of the hypereosinophilic
syndrome; cough, dyspnea, chest pain, skin rash, pulmonary infiltrates, CSF
eosinophilia, splenomegaly and lymphadenopathy, are all common. In approximately
half of the patients eosinophilia is recognized for some time prior to the diagnosis of
LL/L and the leukemia is obscured by the marked eosinophil. The eosinophilia typically
resolves if a complete remission is achieved, only to return as the leukemia relapses.

There are too few cases to B LL/L with the t(5;14) to accurately determine
prognosis but some reports suggest that it is a high risk disease, at least in part
because of the associated hypereosinophilic syndrome. Although about 90% of patients
respond initially to therapy, many relapse and die of LL/L or complications of hypereosinophilia. Death due to cardiac failure occurs in approximately 30% of patients.

**t(17;19)(q21-22;p13), HLF/TCF3 (HLF/E2A).** The t(17;19) is found in less than 1% of cases of B LL/L and although a recurrent translocation in B LL/L because of its infrequency is not presently included in the WHO Classification of LL/L. In this translocation the TCF3 gene on chromosome 19p13 is fused with the bZIP transcription factor gene HLF at 17q21-22. B LL/L with the t(17;19) has no reported distinctive morphologic or immunophenotypic features. Patients are mostly adolescents, often present with hypercalcemia and disseminated intravascular coagulation and have a poor prognosis.

**6q deletions.** Deletions of the long arm of chromosome 6 occur in about 11% of cases of LL/L in children; the majority is associated with other cytogenetic abnormalities. The location of the breakpoint varies but nearly all encompass the 6q21 band. B LL/Ls with deletion of 6q show no morphologic or immunophenotypic specificity. There are no differences in remission induction rates or event free survival in children with or without a 6q abnormality.

**9p abnormalities.** 9p abnormalities are found in approximately 11% of children with B LL/L. In less than 20% of these 9p is the sole abnormality. In the others there is generally a complex karyotype involving multiple aberrations. The majority of cases are pseudodiploid or hypodiploid and only a few have high hyperdiploidy. Deletions of 9p are most frequent (~43%) but add/der(9p), i(9)(q10), translocations and inversions are also observed. Most commonly there is a breakpoint at 9p22 or 9p21-22 the loci of three genes involved in cell cycle regulation (p16^{INK4A}, p14^{ARF}, and p15^{INK4B}), which are missing as a result of the deletion. Most patients (65%) with 9p abnormalities have high-risk clinical features. Event free and overall survival is significantly worse for patients with 9p abnormalities compared to those without. The survival differences are most pronounced for patients with standard clinical risk features.

**Molecular Genetic Abnormalities**

In the past decade numerous new genetic lesions have been identified in both B and T LL/L. These discoveries have expanded knowledge of the pathobiology of lymphoblastic neoplasms and identified several new high-risk genetic alterations. Some of these that have been most extensively studied are included as provisional categories in the WHO Classification of Lymphoblastic Neoplasms and are included in the
Clonal immunoglobulin heavy chain (IgH) gene rearrangements can be detected in about 90% of B LL/L by polymerase chain reaction (PCR). The finding is highly sensitive for B LL/L but has low specificity because IgH rearrangements are also present in many cases of T LL/L and AML. Conversely, T cell receptor (TCR) gene rearrangements are found in 60% of cases of B LL/L. Immunoglobulin light chain gene rearrangements are more lineage specific but lacking in many cases of B LL/L. Gene rearrangement studies are rarely necessary or contributory in the diagnosis of LL/L but may be useful in assessment for minimal residual disease.

* B LL/L with Intrachromosomal amplification of chromosome 21 (iAMP21). iAMP21 is detectable by FISH analysis with a probe that spans the RUNX1 region on the long arm of chromosome 21. The alteration results in multiple extra copies of RUNX1. It is found in approximately 2% of children with B LL/L. Relative to other childhood B LL/L, iAMP21 is associated with a higher median age at diagnosis, a slight female predominance, higher minimal residual disease following induction chemotherapy, a higher incidence of relapse and worse overall prognosis. Recent studies suggest that treatment with high-risk chemotherapy regimens may overcome the adverse prognosis previously attributed to iAMP21 B LL/L.

**IKZF1 deletions.** IKZF1 encodes the lymphoid transcription factor IKAROS, a regulator of B lymphoid development. Deletions of IKZF1 may involve an entire gene or, more commonly, only specific exons. IKZF1 deletions are found in approximately 15% of B LL/L. High-risk associated clinical features are more often present in B LL/L with IKZF1 deletions including higher median age and high presenting leukocyte counts. IKZF1 deletions are present in a high proportion of B LL/L with BCR/ABL1 and often in Down syndrome patients with B LL/L. They are also associated with CRLF2 rearrangements and in Philadelphia chromosome-like (Ph-like) B LL/L (discussed below). Most studies have reported that IKZF1 deletion is an independent predictor of poor outcome.

**Alterations of CRLF2.** CRLF2 (cytokine receptor-like factor 2) is located on the pseudoautosomal regions of the X chromosome. Markedly elevated expression of CRLF2 was found in 14% of children with high-risk B LL/L in one large study. In a majority of cases with rearrangement of CRLF2 there is a translocation of the IGH gene on chromosome 14q32 to CRLF2 in pseudoautosomal region 1 of Xp22.3/Yp11.3. In
most of the remaining cases there is an interstitial deletion of \textit{CRLF2}, resulting in a \textit{P2RY8-CRLF2} fusion. \textit{CRLF2} alterations are strongly associated with the presence of \textit{IKZF1} deletions and \textit{JAK} mutations and are reported to be more common in patients of Hispanic/Latino ethnicity and individuals with Down syndrome. The prognostic significance of \textit{CRLF2} alteration by multivariable analysis is somewhat controversial. The poor prognosis identified in some studies may be attributable to \textit{CRLF2} genomic alterations, specifically \textit{P2RY8-CRLF2} fusion, but not to \textit{CRLF2} overexpression.

\* \textbf{B LL/L BCR/ABL1-like (Philadelphia chromosome-like).} BCR/ABL1-like B LL/L comprises 10\% to 15\% of LL/L in children and increases in prevalence with age to greater than 20\% in adolescents and young adults. These patients respond poorly to standard chemotherapy regimens and are associated with a poor outcome. PBCR/ABL1-like ALL is t(9;22) and \textit{BCR-ABL1} negative but has a gene expression profile with increased expression of hematopoietic stem-cell genes and reduced expression of B-cell-lineage genes, similar to that of \textit{BCR-ABL1} positive B LL/L. \textit{IKZF1} and other B lymphocyte traranscription factor genes are altered similar to \textit{BCR-ABL1} positive B LL/L. A majority of BCR/ABL1-like B LL/L genetic alterations induce activation of kinase signaling pathways; 50\% have \textit{CRLF2} genomic alterations and 25\% concomitant \textit{JAK} mutations. The finding of activated kinase signaling in most cases provides rationale for addition of tyrosine kinase inhibitors to current therapy for these leukemias. Patients with refractory BCR/ABL1-like B LL/L and a \textit{EBF-PDGFRB} fusion reportedly have had a good response to therapy with tyrosine kinase inhibitor drugs.

\textbf{ERG deletion.} ERG intragenic deletions are found in approximately 4\% of childhood B LL/L resulting in a truncated ERG protein; approximately 40\% have and associated \textit{IKZF1} deletion. Patients with \textit{ERG} deletion tend to be older than other children with B LL/L. Aberrant CD2 expression is found in about 40\% of patients. \textit{ERG} deletions are associated with an excellent prognosis with an overall survival of greater than 90\%. Co-association with \textit{IKZF1} does not seem to significantly alter outcome.

\textbf{TP53 mutations.} TP53 mutations are detected in approximately 15\% of patients with LL/L. They are more frequently associated with B than T LL/L and are correlated to low hypodiploidy and MYC-translocations. Alteration of both TP53 alleles is associated with adverse prognosis.

\textbf{Cytogenetic changes at relapse.} Cytogenetic evolution is a common finding at relapse of LL/L. The changes are most frequently related to those at diagnosis; new
structural abnormalities are most common. A new abnormal clone in association with lineage switch is usually indicative of therapy related leukemia.

**Treatment and Prognosis**

**Treatment of B LL/L**

Advances in treatment over the past four decades have dramatically improved the outcome for children with B LL/L. More than 95% of patients achieve complete remission with conventional induction therapy. With central nervous system prophylaxis, post-induction intensive chemotherapy and maintenance therapy of 2 to 3 years, upwards of 80% of children will remain disease free and are presumably cured.

Contemporary treatment protocols for pediatric B LL/L tailor the intensity of therapy to the risk of relapse. Risk of relapse is determined by clinical indicators like age and leukocyte count and biologic features, of which cytogenetics and molecular genetics are most important. Response to treatment, as assessed by rapidity of cytoreduction and detection of minimal residual disease (MRD) are vitally important predictors of eventual relapse. Most patients with low risk indicators, e.g. hyperdiploidy >50 chromosomes and t(12;21), are treated with chemotherapy consisting primarily of drugs with few long-term side effects, such as antimetabolites and L-asparaginase. Patients with higher-risk categories of B LL/L are treated more aggressively with regimens that might include anthracyclines, epipodophyllotoxins, or alkylating agents and tyrosine kinase inhibitors for patients with BCR/ABL1 LL/L. The results for high-risk B LL/Ls are not as good as for low-risk cases but more intensive chemotherapy has improved the remission and survival rates for some of the formerly less favorable types, e.g. t(1;19). The more intensive treatments increase the risk of long-term side effects.

Allogeneic hematopoietic stem cell transplantation is used following first remission in children with the highest-risk categories of B LL/L, e.g. t(9;22) and those with high risk mutations detected by molecular analysis, eg., “BCR-ABL1-like” and often in patients that relapse following standard chemotherapy. Transplantation offers the best chance of cure for these poor prognostic conditions.

Adults with B LL/L are now treated similarly to children but fair less well; fewer achieve long-term event-free survival. This is at least partly because of the greater proportion of high-risk types in adults.

Currently approximately 10 to 20% of children with B LL/L and 25 to 35% with T LL/L are not cured of their disease. Relapsed LL/L remains the 4th commonest
childhood malignancy and the most common cause of cancer deaths in children. Further improvement by dose-escalation of current chemotherapy agents will be limited by toxicities. To improve cure rates further less toxic targeted approaches based on new molecular genetic information will most likely be required.

**Prognostic Indicators in Lymphoblastic Leukemia/Lymphoma**

Numerous parameters have been studied for prognostic significance in LL/L. They may be divided into clinical, immunophenotypic and genetic. The significance of these varies somewhat in different studies. Some of the criteria that are indicators of poor prognosis by univariate analysis lose or have decreased significance by multivariate analysis. For some of the formerly useful indicators improved treatment regimens for high risk LL/L has reduced their prognostic value. The two most important clinical prognostic indicators are patient age and presenting leukocyte count.

**Antigen expression and prognosis.** Expression and lack of expression of some individual antigens have been related to prognosis. CD10(-) B LL/L is a poor prognosis group in infants and adults but is less significant in older children. CD34(+) B LL/L may be an indicator of a favorable prognosis in children but is associated with adverse factors in adults. Strong expression of CD45 and CD20 and lack of CD24 all have been associated with less favorable outcome in children with B LL/L. Expression of CD20 on lymphoblasts in adults with B LL/L appears to be associated with a poor prognosis. Most of these indicators are of minor significance and some of no significance at all with present-day risk stratification therapy.

The importance of myeloid antigen expression on lymphoblasts was controversial until recently. The earliest studies suggested a poorer treatment response and survival for adults with myeloid antigen positive LL/L [My(+) LL/L]. Some studies on children indicated no difference in treatment outcome between My(+) and My(-) LL/L but others reported a worse outcome for My(+). Recent investigations of adults treated with intensive therapy have shown no significant difference between My(+) and My(-) LL/L in response or survival. In children there presently appears to be no difference in treatment response, event free survival or overall survival between My(+) and My(-) LL/L regardless of treatment protocol. Patients with truly biphenotypic leukemias may have a poorer prognosis.

**Minimal Residual Disease (MRD) and prognosis.** Flow cytometry and PCR are the most sensitive of the available methods for detection of MRD and provide
comparable results. Flow cytometry can detect very low levels of leukemic lymphoblasts (0.01 to 0.005%) by identification of a leukemia specific immunophenotype. PCR for gene rearrangements or clone specific translocations or mutations is even more sensitive. Since there is no marker of MRD applicable to all cases ideally a combination of flow cytometry and PCR would seem to be most effective. Most of the data reported by the large cooperative study groups such as the Childrens Oncology Group (COG) are flow cytometry based. Data from numerous studies regardless of techniques used indicate that the level of MRD during clinical remission is a strong predictor of the likelihood of relapse, which in turn is directly correlated with event free and overall survival. No detection of MRD (<1/10,000 cells) at the end of induction chemotherapy is associated with a low relapse rate, whereas, 1% MRD is indicative of a high likelihood of relapse. Similarly no MRD in pre-transplant bone marrow predicts a low chance of relapse, while high levels of MRD (0.1 to 1% blasts) predict a high relapse rate. Despite the apparent value of MRD detection in predicting relapse, the false negative rate is high; less than half of patients that ultimately relapse have detectable MRD after 5 months of treatment.

**Cytogenetic findings and prognosis.** Cytogenetic findings that impart a favorable and unfavorable prognosis have been discussed above in the section on Cytogenetics of this chapter. They are summarized in Table 13.5. All chromosome translocations discovered by conventional metaphase cytogenetic analysis were once thought to impart a poor prognosis but several studies suggest that chromosome translocations per se, with the exceptions of t(9;22) and t(v;11), may not decrease median survival in patients treated by contemporary chemotherapy regimens. More recently identified high risk cytogenetic and molecular genetic alterations such as iamp(21), rearrangement of CRLF2, mutations of IKZF1 and the BCR/ABL1-like gene expression signature are important indicators of high risk B LL/L. Some of these leukemias are potential targets for directed gene based therapies (See section on Molecular Genetics of B LL/L). A two-tier genetic/prognostic classification was recently reported that integrates the eight most commonly deleted genes subordinantly with established chromosomal abnormalities. Two sub-groups with distinct responses to treatment are identified by this approach. In the near future risk-stratification of patients with LL/L may be performed using genomic signatures and clustering algorithms, rather than individual genetic alterations.
**T Lymphoblastic Leukemia/Lymphoma**

The morphological, and cytochemical features of T lymphoblastic leukemia/lymphoma (T LL/L) are similar to those of B LL/L and usually do not definitively distinguish the two. Only features that are distinctive for T LL/L will be detailed below.

**Distinguishing Clinical Features**

The median age of children with T LL/L is higher then for B LL/L and a greater proportion of patients are adults; approximately 80% of patients are male. There is more often significant extramedullary disease; approximately 50% of patients present with a mediastinal mass and lymphadenopathy and organomegaly are more frequent. A greater percentage of T lymphoblastic neoplasms present as lymphoma with minimal or no bone marrow involvement. Relative to B LL/L, there is a higher incidence of CNS disease at presentation (12%) and relapse, the median leukocyte count is significantly higher and there is more often marked leukocytosis (>100X10^9/L).

**Unusual Morphological Variants**

Several of the variant morphological features described for B LL/L may also be observed in T LL/L. These include cytoplasmic granules, hypereosinophilia and mature appearing blasts. A detailed description of these features is found in the discussion of B LL/L. One unusual variant of T lymphoblastic neoplasm that warrants mention is the rare association of T lymphoblastic lymphoma with eosinophilia and myeloid hyperplasia. A t(8;13)(11.2;q11-22) chromosome rearrangement has been identified in some cases. Some of the patients develop AML or myelodysplastic syndrome.

**Immunophenotype**

The lymphoblasts in T LL/L express variable combinations of T cell associated antigens that include CD1a, CD2, CD3 CD4, CD5, CD7 and CD8 as well as several lineage non-specific antigens, especially CD45, CD34 and TdT. In children nearly all cases of T LL/L express one or more of the antigens CD7 (~98%), CD5 (~95%) and CD2 (~92%); concurrent expression of these three antigens is found in nearly 85%. Among these, CD5 is the most specific for T ALL in the diagnosis of acute leukemias but is also found in the B cell neoplasms chronic lymphocytic leukemia and mantle cell lymphoma; CD7 is the most sensitive for T LL/L and CD2 is also quite sensitive but each is expressed in up to 30% of cases of AML. CD3 is the most specific marker for T
lineage leukemia but is lacking on the cell surface in about two thirds of cases of T LL/L; however, virtually all cases express cytoplasmic CD3 (cCD3). CD1a is expressed in 16% to 66% of cases and is not found in B LL/L or AML. CD10 is found in 16% to 57% of cases, much less frequently then in B LL/L. HLADR is seldomly expressed in children with T LL/L but is found in about 10% of cases in adults and in most AMLs that express CD7. Similar to B LL/L, TdT is present in more then 90% of cases but CD34 is found less commonly in children and in only about one third of adult cases. TdT is valuable in distinguishing T LL/L from peripheral T cell neoplasms, which lack TdT but may express any of the other T cell associated antigens except CD1a.

The immunophenotypic profiles of T LL/L bear resemblance to cells in the normal thymus. Cases can be roughly sub-classified into categories corresponding to various stages of thymocyte development. Studies have shown a fairly uniform distribution of T LL/L at early, mid and late thymocyte stages but the lymphoblasts in T lymphoblastic lymphomas less frequently express an early thymocyte immunophenotype. Many cases don’t lend themselves to classification by thymic stage because of asynchronous and aberrant expression of antigens. Furthermore, the clinical and prognostic significance of doing so is controversial.

**Early T-cell precursor LL/L (ETP-LL/L).** ETP-LL/L is a recently described subtype of T LL/L that is defined by a unique immunophenotype and gene expression profile. The defining features of the immunophenotype are cytoplasmic CD3(+), CD1a(-), CD8(-), CD5(-/+weak) with stem cell and myeloid markers. The stem cell and myeloid markers are variable and may include expression of CD34, HLA-DR, CD117, CD13, CD33, CD11b, CD65 and possibly others but never myeloperoxidase. The immunophenotype and gene expression signature differ from other T LL/L and are similar to normal early T-cell precursors. These normal counterparts to ETP-LL/L are a subset of thymocytes that have recently migrated from the bone marrow to the thymus and maintain the potential for multilineage differentiation suggesting direct derivation from hematopoietic stem cells.

ETP-LL/L comprises 12 to 15% of T LL/L and occurs in both children and adults; the median age is higher for ETP-LL/L than for other T LL/L. There appears to be no other distinctive clinical findings or morphologic features of the blasts that distinguish ETP-LL/L from other T LL/L.

Cytogenetic abnormalities are frequent and vary widely with no recurrent
abnormality detected. Reportedly del(13q) is found more frequently than in other T LL/L. ETP-LL/L exhibits a marked degree of genomic instability exceeding that of any other type of LL/L.

Recognition of ETP-LL/L is important because of its association with a delayed leukemic cell clearance, high incidence of MRD following contemporary protocols of intensive chemotherapy, high rate of relapse and in some studies a poorer overall survival than for other T LL/L. Among 17 patients with ETP-LL/L in one study the 10 year overall survival was 19%, event-free survival 22% and 10-year relapse rate 72%. Some more recent reports indicate higher MRD and relapse rate but no significant difference in overall survival from other T LL/L.

**Genetics**

Fifty to 60% of cases of T LL/L have an abnormal karyotype. In contrast to B LL/L where cytogenetic findings often trigger therapy adjustments, in T ALL cytogenetics does not provide risk group categories or dictate therapy modifications. For this reason no cytogenetic categories of T LL/L are included in the WHO Classification. The recurring translocations of B LL/L are rarely observed in T LL/L; hyperdiploidy >50 is also relatively uncommon and is not associated with survival advantage. Conversely, the two most common translocations in T LL/L, [t(11;14) and t(10;14)] are virtually never observed in B LL/L.

In about one third of cases of T LL/L translocations involve the \( \alpha/\delta \) T-cell receptor loci at, 14q11-q13 or the \( \beta/\gamma \) loci at 7q34; a variety of partner genes may be involved. Abnormalities involving 14q11-13 occur in approximately 20% of karyotypically abnormal cases; t(11;14)(p13;q11) and t(10;14)(q24;q11) are the most common but other balanced and unbalanced translocations, deletions and inversions are also observed. In the largest series of karyotyped cases of pediatric T LL/L 2.8% of all cases and ~5% of those with cytogenetic abnormalities were near tetraploid. This small group of patients is likely to be above the median age, have large lymphoblasts, and a poor prognosis.

A few other clinical and prognostic relationships to cytogenetic findings have been made. Actuarial 5-year event free survival for patients with a normal karyotype is 62% compared to 51% for those with an abnormal karyotype. Better survival also appears to be associated with a t(10;14); worse survival is associated with the presence
of any derivative chromosome. A higher leukocyte count is associated with a t(11;14) [median=407X10/L] and a lower one with hyperdiploidy >50 or loss of chromosome 5q material. Patients with any kind of a derivative chromosome tend to be older and t(11;14) may be associated with a younger age. A higher proportion of boys (5:1) are found among cases with a t(10;14). Alterations of chromosome 6q have been shown to be associated with high-risk disease.

**Molecular genetics of T LL/L.** Clonal T cell receptor (TCR) gene rearrangements can be detected in most cases of T LL/L by PCR or Southern blot analysis. Presence of clonally rearranged TCR genes is a sensitive indicator but lacks specificity since they are found in many cases of both B LL/L and AML; their value in lymphoblastic neoplasms is mostly in detection of MRD.

T LL/L patients cluster into several groups characterized by differential gene expression profiles. These patterns of gene expression have provided a number of insights on the pathobiology of T LL/L and have identified T LL/L subtypes that seem to have prognostic significance. Gene expression profiling along with immunophenotyping and single nucleotide polymorphism-array data identified the clinically important high-risk T LL/L sub-type, early T cell precursor LL/L (ETP-LL/L) described above in the section on Immunophenotype.

Numerous studies suggest that somatic gene mutations play a role in T ALL pathogenesis. Several candidate genes have been identified that seem to be involved in T LL/L patho-mechanisms. These include NOTCH1, FBXW7, CDKN2A, BCL11B, FLT3, WT1, PTPN2, PHF6, and NRAS. The two genes that have been most extensively studied in T LL/L are NOTCH1 on chromosome 9q34.3 and FBXW7 on chromosome 4q31.3. These genes are critical to normal T cell development, proliferation and maturation. Mutations of NOTCH1 occur in 34 to 71% and FBXW7 mutations in 8.6 to 16% of cases of T LL/L. These mutated genes result in increased NOTCH1 activity and overexpression of downstream targets, which impair cell cycle control and can lead to development of a T lymphoblastic neoplasm. Mutations of NOTCH1 and FBXW7 have been associated with a favorable prognosis in T LL/L (see section on Treatment and Prognosis, below).

**Treatment and Prognosis**

Major improvement in treatment response in T LL/L has been achieved in recent
years. It has resulted from use of highly intensive therapeutic regimens, e.g., four drug induction and multidrug continuation including doxorubicin and prednisone, with prophylaxis for CNS disease and high-dose L-asparaginase. Most studies have shown improvements in both event free and overall survival. Some investigations indicate that current risk for patients with T LL/L treated intensively is similar to that of B LL/L, with 3-year survival rates up to 78.8% and 7-year event free survival of 70%. Still, most studies of children have shown poorer outcomes for T compared to B LL/L. This is at least partly related to the greater incidence of high-risk clinical features, e.g., older than 10 years, high presenting leukocyte counts, lymphomatous presentation. Adult patients with T LL/L fair better than those with B LL/L, although in neither are outcomes comparable to those in children.

Clinical high risk features discussed for B LL/L generally also apply for T LL/L, high leukocyte counts, age >15 years, mass disease, etc (See section on Prognostic Factors in B LL/L). Minimal residual disease detection following induction chemotherapy is also an important a predictor of relapse in. In addition there are immunophenotypic markers and cytogenetic features unique for T LL/L that impact prognosis. There is a diversity of data regarding the prognostic importance of immunophenotype in T LL/L. Most studies have shown no differences in survival related to thymic stage. Some, however, suggest that cases with an intermediate stage thymocyte immunophenotype, CD1(+) CD4(+), CD8(+) fair the best and early and late [surface CD3(+)] thymocyte stages are less favorable. Early precursor T LL/L, discussed above, is associated with post-induction MRD and relapse and shortened overall survival in some studies. These findings suggest that intensification of treatment and alternative therapies including hematopoietic stem cell transplantation in first remission are required for ETP-LL/L. However, with more favorable treatment/survival results recently reported, experimental treatments for ETP-LL/L may not always be required.

There are variable results regarding the prognostic importance of expression of individual antigens. Expression of CD10 has been associated with good outcome in some studies but not in others. Lack of expression of CD5 has been an indicator of unfavorable event free survival.

Cytogenetic findings do not define prognostic groups as clearly as for B LL/L. Their prognostic implications in T LL/L are discussed in the section on Cytogenetics.
Gene expression signatures are shown in some reports to be associated with prognosis but gene expression analysis as a regular clinical tool for risk-stratification in T LL/L will require solving technical and cost challenges. Also, additional confirmation of its value in large clinical studies is to be determined.

Mutations of NOTCH1 and FBXW7 appear to be associated with a favorable prognosis in T LL/L depending on the applied therapeutic protocol. Loss of heterozygosity at chromosome 6q (LOH6q) is reported to be associated with increased relapse risk and unfavorable prognosis. These molecular markers appear to have potential for a role in risk stratification in T LL/L and possibly for future targeted therapies.

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I. Juvenile Myelomonocytic Leukemia (JMML)
   1. Epidemiology and Clinical Features
      a. Uncommon (1.3 per million children per year, 2-3% of all childhood hematologic malignancies)
      b. Patients with neurofibromatosis type 1 (NF-1) have a propensity to develop JMML
      c. Most cases (75%) occur in children <3 years of age; boys are affected more commonly than girls
      d. Patients commonly present with constitutional symptoms or evidence of infection, also with signs of bleeding; there is usually marked hepatosplenomegaly
      e. JMML is aggressive and fatal if left untreated (death often due to organ dysfunction from leukemic infiltrate)
      f. Predictors of short survival include older age (> 2yrs), lower platelet count (<33 x 10^9/L), and levels of HbF≥10%
   2. Morphologic Features
      a. Peripheral blood
         i. Leukocytosis, thrombocytopenia, and often anemia
         ii. Median WBC 25-30 x 10^9/L, rarely exceeds 100 x 10^9/L
            1. Leukocytes = neutrophils with left-shift and monocytes
            2. Blasts are usually <5% and always <20% (no Auer rods)
            3. nRBCs often seen
      b. Bone marrow
         i. Hypercellular with (usually) granulocytic proliferation
         ii. Monocytes usually 5-10% of bone marrow differential
         iii. Blasts are always <20% (no Auer rods)
         iv. Dysplasia may be present but minimal
      c. Extramedullary infiltrates
         i. Spleen, liver, lung, skin, gastrointestinal tract, lymph node
   3. Immunophenotypic findings
      a. No specific immunophenotypic abnormalities
4. Other features
   a. GM-CSF hypersensitivity (and resultant hyperphosphorylation of STAT5)
   b. Markedly increased synthesis of fetal hemoglobin (HbF)

5. Genetics
   a. Normal karyotype (65%), monosomy 7 (25%), other chromosomal abnormalities (10%)
   b. Philadelphia chromosome and BCR-ABL1 fusion are absent
   c. Mutations in NF1, PTPN-11, K-RAS, N-RAS, and CBL are detected in 90% of patients (mutations are largely mutually exclusive); these genes all encode proteins that signal through the RAS-RAF-MAPK pathways
   d. Additional gene mutations are uncommon
      i. SETBP1 and JAK3 were most frequent secondary mutations

6. Diagnostic criteria
   a. Has been revised over time with advances in understanding of molecular pathogenesis
   b. Will be updated in the 2016 revision to the WHO classification of hematological malignancies (see references 1&2 and will be discussed during lecture)

7. Important diagnostic considerations
   a. Human herpesvirus infections, leukocyte-adhesion deficiency, infantile malignant osteopetrosis, hemophagocytic lymphohistiocytosis (HLH), and Wiskott-Aldrich syndrome (mutational analysis helpful in exclusion of these entities)
   b. Transient myeloproliferative disorder in children (neonates/early infants) with Noonan syndrome (germline mutations of PTPN11, K-RAS or N-RAS)
      i. Myeloproliferative disorder that generally resolves spontaneously

8. References (1-8)

II. Myeloid proliferations related to Down syndrome (DS)

1. Transient abnormal myelopoiesis (TAM) AKA transient myeloproliferative disease (TMD)
   a. Occurs in approximately 5-10% of DS newborns
   b. Usually diagnosed at birth to 7 days
c. Patients can be asymptomatic or, less commonly, present with jaundice and bleeding diatheses, respiratory distress, ascites, pleural effusion, heart failure, and skin infiltrates
d. Presenting features include thrombocytopenia with atypical platelets; leukocytosis (often marked); basophilia; circulating erythroblasts and anisopoikilocytosis; hepatosplenomegaly can be present
e. Blasts frequently have features suggestive of megakaryoblasts and have a characteristic immunophenotype (positive for CD13, CD34, CD33, CD41, CD56, CD61, CD117, glycophorin A, and frequently CD7 and CD36); erythroid and megakaryocytic dysplasia often present in bone marrow
f. Acquired GATA1 mutations are present in blast cells of TAM
g. Most cases have spontaneous remission in 2-14 weeks
h. There is a mortality rate of around 20% associated with TAM
i. Non-transient AML develops 1-3 years later in 20-30% of these children

2. Myeloid leukemia associated with Down syndrome
   a. 1-2% of children with DS will develop AML during the first 5 years of life
   b. Occurs in 20-30% of children with a prior history of TAM (usually 1-3 yrs after TAM)
   c. Usually acute megakaryoblastic leukemia
   d. Similar morphologic features as TAM; bone marrow core may show dense network of reticulin fibers (dry tap)
   e. Leukemogenesis is multi-step (GATA1 mutation alone is insufficient)
   f. Trisomy 8 is common, monosomy 7 is rare
   g. Very favorable prognosis compared to non-DS children with AML
   h. Children should be treated on DS-specific protocols
   i. Children with DS > 5 yo with myeloid leukemia may not have GATA1 mutations and such cases should be considered as “conventional” MDS or AML

3. References (1, 9-13)
III. Acute Megakaryoblastic Leukemia (AMKL)

1. AMKL is much less likely in children without DS (AMKL comprises 3-6% of AML in children without DS)

2. AMKL arising in non-DS patients has a poorer prognosis

3. If contains the t(1;22)(p13;q13), the AML should be classified under AML with recurrent cytogenetic abnormalities
   i. “AML with t(1;22)(p13;q13)(RBM15-MKL1)”
   ii. Most commonly occurs in infants without DS (median age at diagnosis 4 months)
   iii. May present as a soft-tissue mass!

4. If does not contain the t(1;22)(p13;q13), and does not meet criteria for other classification (ie for t-AML or AML-MRC), then the AML should be classified under AML, NOS.
   i. Very uncommon
   ii. Occurs in both adults and children

5. References (10, 14)
IV. References