Lymphoblastic lymphoma (LBL) is a highly aggressive neoplasm of T-/B-precursors resembling acute lymphoblastic leukemia, with no or limited bone marrow involvement (<25%), that develops more frequently in children and young adults and is typically characterized by a grossly enlarged mediastinum, and whose diagnostic hallmark is the expression of a T-/B-precursor cell immunophenotype, the T-cell subset accounting for 90% of all cases. The adoption of pediatric-derived, intensive lymphoblastic leukemia-like protocols led to significantly improved results, with survival rates of about 70% and 90% in adults and children, respectively. Adequate central nervous system prophylaxis and mediastinal irradiation contributed to the therapeutic success; however, the role of radiation therapy is debated due to toxicity concerns and the excellent results obtained with radiation-free programs especially in pediatric patients. With these modern schedules, localized radiotherapy and/or hematopoietic stem cell transplants could be generally omitted, and considered only for high-risk patients identified through postinduction computed tomography/positron-emission tomography scans, minimal residual disease analysis, and new genetics and genomics. New clinical studies will have to confirm the value of these assays for risk-oriented therapy, while further therapeutic progress is expected from the introduction of new drugs and targeting agents.

**Epidemiology**

LBL is a rare disease for which specific incidence data are missing. A population-based study from Sweden between 2000 and 2009 identified 39 new LBL cases without showing incidence data (3). Contrary to ALL, in which only 20–25% of the cases express a T-cell phenotype, LBL belongs more often to the T- rather than B-cell lineage, with an approximate ratio of about 9:1. In a large adult series of 607 T-ALL/LBL cases from Germany, 101 had T-LBL (16.6%) (4). Thus, the overall incidence of LBL is expected to be less than 10% out of a total ALL/LBL figure estimated at 1.3/100 000 annually (5, 6). T-LBL occurs more frequently in late childhood, adolescence, and young adulthood, with a male predominance of 2:1 or greater. B-LBL is exceedingly rare.
Biology of disease

Pathogenesis and molecular pathogenesis

Risk factors and pathogenetic factors for LBL are mostly unknown (2). In some recent studies, a variety of deregulated (onco)genes, primarily NOTCH1 and several other genes affecting mechanisms of T-cell growth and differentiation/proliferation control, were found to play a pathogenetic role in T-ALL/LBL (7). Studies including thymic samples from both experimental animals and humans showed significant genetic alterations in transformed T-precursor cells, concerning mini-chromosome maintenance proteins (8), miRNA-30a, miRNA-141, miRNA-139b, the SMO gene (9), and the FAS system (10) other than altered expression of NOTCH1, FBXW7, and of the many other genes associated with T-ALL/LBL (7).

LBL vs. ALL

Once the disease is established, the main difference of T-LBL vs. T-ALL lies in the minimal or absent BM contamination by T lymphoblasts in the former. Along with an enlarged thymic/mediastinal mass (90% of the cases), this generates a unique clinical pattern, regardless of the involvement of other organs and tissues. The difference would have a biologic basis. In a zebrafish model, overexpression of BCL-2 in association with Myc resulted in T-LBL rather than T-ALL, with increased SIP1 and ICAM1 signaling, increased autophagy, cell–cell adhesion, and decreased tumor cell intravasation (11). In another study, the expression of the promyelocytic leukemia zinc-finger (PLZF) transcription repressor increased the risk of BM involvement by T-lymphoma cells (96% vs. 39%, \( P = 0.000 \)) and was mutually exclusive with the expression of CD1a, CD4, CD8 antigens, and the T-cell receptor beta (TRB) F1 (12). It was concluded that PLZF+ early immature double-negative cells but not PLZF− cells are responsible for BM involvement in T-ALL/LBL.

Gene expression profiling (GEP), next-generation sequencing (NGS), and whole exome sequencing (WES) studies revealed other differences among the two disease subsets. Early GEP studies in pediatric T-LBL suggested upregulation of genes involved in cell adhesion (13, 14), a partially T-LBL-specific gene signature affecting genes involved in chemotaxis (downregulated ARRB2: reducing chemotaxis) and angiogenesis (upregulated EPAS1, PTPRB, SLIT2: promoting angiogenesis for local tumoral growth in lymph nodes), and other differences in genomewide copy number alteration profile (15). In a small series of 5 T-LBL pediatric patients studied with NGS/WES (16), 45 genes were exclusively identified in T-BL but not T-ALL, some of which had high functional relevance. Data relative to B-LBL are scanty. Again, it was postulated that differences with B-precursor ALL might be related to overexpression of genes encoding for chemokine receptors CXCR4 and its ligand, or other adhesion molecules involved in extramedullary migration and homing (17).

Cytogenetics

Due to its rarity, there is very little information on cytogenetic abnormalities in LBL (17). A commonly reported abnormality would be the presence of additional chromosome 21 material, which is rare in ALL, in form of trisomy, tetrasomy, or add(21)(q22) (2). However, in B-LBL, 16 of 26 evaluable cases had a normal karyotype, 5 had hyperdiploidy and 5 had other structural abnormalities without abnormal chromosome 21 (18). In T-LBL, frequent (50–70%) cytogenetic abnormalities involve the 14q11-13 region (T-cell receptor alpha [TRA]/delta [TRD] genes), including inv(14)(q11:q32), and chromosomes 9, 10, and 11. Rearrangements involving TRB (7q34) and TR gamma (TRG; 7p14.1) genes are also common (2). In the largest cytogenetic study in T-LBL (19), 55% of 56 evaluable cases had an abnormal karyotype, including pseudodiploidy (25%), various chromosome deletions (20%), hyperdiploidy, and chromosome translocations (18%) each, with many cases of structural abnormalities and translocations involving the 9q34 region (16% and 5% each). One patient had t(9;17) (q34;q23), which is associated with a mediastinal mass without BM involvement. This translocation is typical of T-LBL, and translocations involving 9q34 are significantly more common in T-LBL than T-ALL (\( P = 0.000 \)) (19).

Cases of T-LBL associated with myeloid hyperplasia or hypereosinophilia have been reported in association with t (8;13)(p11;q11) in the so-called 8p11 myeloproliferative syndrome (20). The underlying genetic lesions of these rare clinical variants are examined below.

Genetics

LBL, like ALL, is characterized by clonal rearrangements of immunoglobulin (Ig) heavy- and light-chain genes and TR genes. Cross-lineage rearrangements can be detected (immature IgH rearrangements in T-LBL and TR gene rearrangements in B-LBL), with B-LBL defined by mature Ig rearrangements involving the variable regions (21). These patient-specific rearrangements may be used to generate molecular probes for the study of minimal residual disease (MRD). In T-LBL, the type of TR gene rearrangement may influence the clinical course. A French study including both adults and children identified three different TR gene rearrangement subsets (immature: no TR or incomplete TRD rearrangement; mature: biallelic TRD deletion and both TRG and TRB rearrangement; intermediate: TRD, TRG, and TRB rearrangement), with an associated overexpression of HOX11/TLX1 and HOXA9 transcripts in the intermediate TR group (22). The immature TR subset correlated with the risk...
of BM involvement, whereas intermediate/mature groups were associated with a predominantly thymic presentation. The BFM Group analyzed a large series of pediatric patients with T-LBL, reporting NOTCH1 mutations (clinically favorable) in 60% and FBXW7 mutations in 18% of 116 evaluable cases, and loss of heterozygosity at chromosome 6q (LOH6q, clinically unfavorable) in 25 of 207 cases (12%) (23). A subsequent French study confirmed the occurrence of NOTCH1/FBXW7 mutation in 55% of 54 patients with T-LBL and identified FLASH gene deletion at chromosome 6q as a further molecular marker detectable in 18% (24). In a most recent analysis of 49 adult patients with T-LBL, the cooperative GRAALL study group reported on the expression of a 4-gene prognostic classifier (NOTCH1, FBXW7, N/K-RAS, and PTEN, see below) (25).

In rare cases, T-LBL is associated with myeloproliferative disorders ranging from the 8p11 myeloproliferative syndrome to an hypereosinophilic syndrome to a subacute or acute myelomonocytic leukemia. Gene abnormalities detectable in both T-LBL and the myeloid compartment included rearrangements of FGFR1 (26) and PDGFRα/B (27) genes. Cases harboring PDGFRα/B gene rearrangement and the few ones displaying the NUP214-ABL rearrangement (22) may be susceptible to the therapeutic effects of tyrosine kinase inhibitors (TKI) such as imatinib and others. This also applies to the very rare but well-documented cases of T-LBL carrying the BCR-ABL translocation, described in past as lymphoblastic crisis of Philadelphia chromosome-positive ALL.

Diagnosis

Histopathology

Adequate diagnostic specimens from involved organs are needed to establish a diagnosis of LBL. Small biopsies even from large masses must be avoided because they are difficult to interpret, sometimes requiring a repetition which may cause treatment delay. The biopsy confirms a diffuse proliferation of lymphoblasts indistinguishable from ALL cells. Principles of diagnostic pathology and differential diagnosis were detailed elsewhere (1, 2). In essence, LBL subtypes with convoluted or non-convoluted nuclear profile were recognized, as well as a pleomorphic variant of larger ALL-like cells. The differential diagnosis is with other hematologic malignancies of B-cell origin, such as large cell lymphoma, the blastic subtype of mantle cell lymphoma, and others and is mainly based on the immunophenotypic and immunohistochemical characteristics of the disease.

Immunophenotype

The mainstay of LBL diagnostics is represented by the immunophenotypic analysis. Together with the study of genetics/cytogenetics, this ensures a safe diagnosis of LBL ruling out other lymphoid and non-lymphoid malignancies (1, 2). Biopsy specimens or adequate LBL cell samples from pleuroperticardic effusions or other body fluids are suitable to immunophenotypic analysis through immunohistochemical staining and/or multiparameter flow cytometry.

B-LBL is always positive for B-cell markers CD19, CD79a, and CD22. CD10 (common ALL antigen), CD 24, PAX5, and terminal deoxynucleotransferase (TdT) are expressed in most cases, while the expression of CD20 and the stem cell antigen CD34 is variable and CD45 may be absent. A large retrospective review on 146 LBL cases employed a predefined immunostaining panel (CD20, CD79a, PAX5, CD19, CD10, IgM, CD3, CD1a, CD4, CD8, CD5, CD2, MPO, TdT, CD34), using EGIL criteria to classify LBL subsets (28).

Of 42 B-LBL, none expressed a pro-B phenotype (CD79a/CD19+ only), 20 were CD10+/IgM− (common type), 5 were CD10+/IgM+ (pre-B) and 17 lacked a reliable IgM immunostaining (of which 15 were CD10+). Because CD79a may be expressed by some T-LBL, two B-markers were required to prove B-lineage commitment. PAX5 was much more sensitive than CD20 (100% vs. 35%). CD22 could be added to increase the panel sensitivity and specificity for B-LBL. TdT negativity was occasionally observed, and it does not exclude LBL.

In the group of 90 T-LBL, there were 49 cases with cortical CD1a+ phenotype, 35 cases of non-cortical phenotype (CD1a−, CD3+), and 6 cases with insufficient characterization for subtype attribution. The assessment of cytoplasmic and surface CD3 positivity, as used by the EGIL group to differentiate CD1a− pre/pro-T-ALL (cCD3+, sCD3−) from mature T-ALL (cCD3+, sCD3+), was not reliable enough using the immunohistochemical staining. However, cortical T-LBL was more often double CD4+/CD8+ than non-cortical, whereas no difference was noted as regards expression of CD34 and CD10. Eleven LBL expressed mixed-lineage phenotype (7 myeloid/B-cell, 2 myeloid/T-cell, 2 B/T-cell), and 3 cases were undifferentiated expressing only very early hematopoietic cell markers (TdT, CD10). Another large study examined the immunophenotype of 180 cases of T-LBL, including flow cytometry other than immunohistochemical staining (29). Also in this study about 10% of the cases lacked expression of TdT but were concurrently CD79a+, or expressed myeloid antigens CD33/CD13 or CD34. Altogether, 24 cases expressed an early T-cell phenotype (CD1a−, CD8+, CD5+ [weak], with or without CD34 and CD33) or a pro-thymocyte phenotype (CD1a−, CD8−, CD5+−, CD34− and CD33), while the majority expressed a subcapsular (CD1a+, CD4+ and CD8+n = 56) or cortical (CD1a+, CD4+ or CD8+n = 66) thymocyte profile. This differs from the EGIL schema, in that the expression of s/cCD3 is not used for the identification of the mature-T subset (cCD3+, sCD3+) vs. the pre/pro-T subsets (cCD3+,
sCD3−) in CD1a− cases. Cases of early-T phenotype had a low risk of mediastinal involvement (5%, \( P = 0.031 \)) but were associated with higher risk of disseminated BM disease (≥1% by flow cytometry, \( P = 0.0001 \)).

**Clinical presentation and staging**

**Clinical presentation**

LBL occurs more commonly in children and male patients, and although T- and B-cell LBL are morphologically indistinguishable, the clinical presentation can suggest a different disease biology. The most frequent sites of involvement observed in adults and children are summarized in Tables 1 (18, 30–37) and 2 (3, 25, 38–47).

A mediastinal mass is the most typical localization of a T-cell LBL. The mediastinal involvement is often massive, with a bulky enlargement associated with bilateral pleural and pericardial effusion. Most patients report dyspnea, cough, and chest pain, due to the progressive airway obstruction and a superior vena cava syndrome. In patients with nodal presentation, swollen lymphadenopathies develop in cervical, supraclavicular, and axillary regions. Abdominal involvement is rarer, but when present, it affects primarily the liver and spleen. A central nervous system (CNS) involvement is uncommon at presentation (3–9%), except for patients with BM involvement, in whom incidence is higher. CNS is often the first site of relapse. Testes and ovaries may be involved and may also represent a site of relapse.

B-LBL exhibits a distinctive clinical picture. Unlike T-LBL, a mediastinal mass is rare, whereas lymph nodes and other extranodal sites are frequently involved (2). An extranodal site can be the only manifestation of the disease, as other extranodal sites are frequently involved (2). An extranodal involvement is more commonly on the scale, face, and neck, are increasingly reported (48).

**Staging procedures**

The assessment of the disease extent is the same as for other aggressive lymphomas and includes evaluation of BM (cytology and histology) and cerebrospinal fluid cytology for the detection of BM (<25% blast cells in LBL) and CNS involvement. Supplemental flow cytometry may disclose foci of occult BM disease (reviewed below). A computed tomography (CT) scan of chest and abdomen and a 18fluorodeoxyglucose positron-emission tomography (PET) assay are used to confirm initial sites of disease, while magnetic resonance imaging (MRI) is useful for a suspect involvement of the spine, skull, and brain structures, or the heart. The staging system most often used in pediatric LBL is that developed at St. Jude’s Hospital (34), devised to reflect more accurately the extent of disseminated disease, contiguous lymphnodal involvement, and unresectable masses, while the classical Ann Arbor staging system is more typically used in adult patients (2). Initial patient evaluation is completed with the analysis of blood counts and serum LDH concentration, and tests of liver and kidney function.

**Response assessment and risk factors**

**Clinical response evaluation**

Postinduction response evaluation aims at identifying the patients requiring salvage therapy and depends on protocol design for timing of response assessment, that is after one or two chemotherapy courses (e.g., induction I and II in BFM studies); however, it follows some basic principles in accordance with Cheson criteria, based on CT scan evaluation for

<table>
<thead>
<tr>
<th>Table 1 Sites of involvement in pediatric LBL</th>
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<tbody>
<tr>
<td>Reiter et al. (29)</td>
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<tr>
<td>-------------------</td>
</tr>
<tr>
<td>No. of patients</td>
</tr>
<tr>
<td>Involving sites</td>
</tr>
<tr>
<td>Mediastinum</td>
</tr>
<tr>
<td>Pleuropericardic</td>
</tr>
<tr>
<td>Lymph nodes</td>
</tr>
<tr>
<td>CNS</td>
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<tr>
<td>BM (&lt;25%)</td>
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<tr>
<td>Bone</td>
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<tr>
<td>Gonads</td>
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<tr>
<td>Head and neck</td>
</tr>
<tr>
<td>Kidney</td>
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<tr>
<td>Digestive tract</td>
</tr>
</tbody>
</table>

CNS, central nervous system; BM, bone marrow.

1 B-LBL only.
intrathoracic and abdominal disease (49). With these criteria, a complete remission (CR) was defined as normalization of any abnormal lymphadenopathy, with a longest transverse diameter not exceeding 1.5 cm, while the designation of unconﬁrmed CR (CRu) was adopted for patients with a tumor size reduction >75%. PET scan evaluation was encouraged. The assessment of mediastinal reduction in T-LBL is of the utmost importance. In the pediatric BFM study (30), a complete chest X-ray clearing on Day 33 (induction I) was considered a CR. Non-CR patients had a CT: in those with 70% or greater tumor reduction treatment was unmodiﬁed, whereas it was intensiﬁed in case of less than 70% reduction (high-risk). A subsequent CT/MRI reassessment led to mediastinal biopsy for further therapeutic decisions in patients not achieving CR.

PET assessment
An imaging technique with high sensitivity and speciﬁcity such as PET might be important for the postinduction detection of viable mediastinal tumors, allowing to plan MRT or other intensiﬁcation therapy without the need of invasive surgical procedures. In a population-based retrospective analysis, PET did not predict long-term outcome. However, the patient number was small, PET was not available at baseline and was not uniformly performed during treatment (3). The question was addressed with better methodology by two recent studies. In the GMALL trial postinduction, PET results were signiﬁcantly associated with the response obtained after consolidation 1 (PET+: 0/21 CRu vs. 10/22 PR; [partial remission], P = 0.001), suggesting an equivalent informative value of PET-negative CRu in predicting an equivalent outcome (25); however, PET results correlated with normalization of BM morphology following anthracycline-based chemotherapy. Minimal disseminated and residual disease (MDD/MRD) is easily detectable in patients initially staged as BM negative (MDD) and/or with normalized BM morphology following induction/consolidation therapy (MRD). Therefore, evaluation of both MDD and MRD can reﬁne the staging procedure, just as TdT+ cells in BM and/or blood samples in 57% of 70 pediatric T-LBL patients with a substantially different risk of relapse among those without a complete remission (15). With these criteria, an abnormal lymphadenopathy (CRu) was deﬁned as normalizing of any abnormal lymphadenopathy, with a longest transverse diameter not exceeding 1.5 cm, while the designation of inconclusive CR (CRu) was adopted for patients with a tumor size reduction >75%. PET scan evaluation was encouraged. The assessment of mediastinal reduction in T-LBL is of the utmost importance. In the pediatric BFM study (30), a complete chest X-ray clearing on Day 33 (induction I) was considered a CR. Non-CR patients had a CT: in those with 70% or greater tumor reduction treatment was unmodiﬁed, whereas it was intensiﬁed in case of less than 70% reduction (high-risk). A subsequent CT/MRI reassessment led to mediastinal biopsy for further therapeutic decisions in patients not achieving CR.

Minimal disseminated and residual disease

<table>
<thead>
<tr>
<th>Involved sites</th>
<th>Hoelzer et al. (37)</th>
<th>Le Gouill et al. (38)</th>
<th>Thomas et al. (39)</th>
<th>Jabbour et al. (40)</th>
<th>Song et al. (41)</th>
<th>Cortelazzo et al. (42)</th>
<th>Bersvendsen et al. (43)</th>
<th>Wang et al. (44)</th>
<th>Ellin et al. (3)</th>
<th>Goekbuget et al. (45)</th>
<th>Lepretre et al. (24)</th>
<th>Xie et al. (46)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>45</td>
<td>92</td>
<td>33</td>
<td>27</td>
<td>34</td>
<td>30</td>
<td>25</td>
<td>36</td>
<td>30</td>
<td>149</td>
<td>148</td>
<td>57</td>
</tr>
<tr>
<td>Mediastinum</td>
<td>91%</td>
<td>65%</td>
<td>70%</td>
<td>100%</td>
<td>82%</td>
<td>70%</td>
<td>89%</td>
<td>72%</td>
<td>90%</td>
<td>93%</td>
<td>95%</td>
<td>39%</td>
</tr>
<tr>
<td>Pleuropericardic</td>
<td>40%</td>
<td>49%</td>
<td>30%</td>
<td>44%</td>
<td>44%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7%</td>
<td>5%</td>
<td>2%</td>
<td>5%</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>71%</td>
<td>49%</td>
<td>42%</td>
<td>33%</td>
<td>–</td>
<td>–</td>
<td>33%</td>
<td>–</td>
<td>79%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>CNS</td>
<td>–</td>
<td>26%</td>
<td>9%</td>
<td>15%</td>
<td>15%</td>
<td>–</td>
<td>–</td>
<td>20%</td>
<td>0%</td>
<td>5%</td>
<td>2%</td>
<td>5%</td>
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<tr>
<td>BM (&lt;25%)</td>
<td>31%</td>
<td>22%</td>
<td>15%</td>
<td>44%</td>
<td>21%</td>
<td>40%</td>
<td>12%</td>
<td>25%</td>
<td>23%</td>
<td>18%</td>
<td>18%</td>
<td>30%</td>
</tr>
<tr>
<td>Liver/spleen</td>
<td>15%</td>
<td>–</td>
<td>0%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>69%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Skin/subcutaneous</td>
<td>2%</td>
<td>12%</td>
<td>–</td>
<td>3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2%</td>
<td>11%</td>
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<td>–</td>
</tr>
<tr>
<td>Bone</td>
<td>2%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>5%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
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<tr>
<td>Gonads</td>
<td>–</td>
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<td>–</td>
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<tr>
<td>Head and neck</td>
<td>2%</td>
<td>–</td>
<td>–</td>
<td>3%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>1%</td>
<td>11%</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Kidney</td>
<td>2%</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>2%</td>
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</table>

CNS, central nervous system; BM, bone marrow.
MDD (0/33, 0%) and MDD >10^{-3} (8/24, 33.3%) (52). Molecular MDD was evaluated in a French pediatric study (24), in which 10 of 23 patients were found to harbor MDD (43.4%), including 4 of 17 with stage II–III disease (23.5%). Prognostic correlations have not been evaluated. The only study to evaluate MRD was the NILG adult trial (42), in which 11 patients were evaluated molecularly, 5 of whom were MRD positive (45.4%). These were considered high-risk patients and selected for stem cell transplantation (SCT).

**Risk factors**

Contrary to ALL, strong and uniform prognostic factors were not established for LBL. In the pediatric setting (Table 3) (18, 30–37, 53), some authors reported a better outcome for patients younger than 10 yrs (14, 33, 34, 36) while data regarding gender were heterogeneous (33, 36). Among disease-related factors, advanced stage and CNS involvement played an adverse role in some series (18, 36, 54) although in one study, stage IV patients fared unexpectedly better than stage III patients (37). However, in most childhood series, no prognostic factor was identified following the introduction of highly effective ALL-type chemotherapy. In adult LBL (Table 4) (3, 25, 38–47, 55), the favorable prognostic factors were young age (<40 yrs) (45), female gender (46), low international prognostic index (IPI) score (47), B-cell phenotype, and lack of BM or CNS involvement (39–41). Regarding response to ALL-type chemotherapy, some underlined the importance of an early CR (46, 47, 56), while others did not, including two recent large series from GMALL and GRAALL-Lysa (25, 44). As shown previously, MDD and MRD could become new valid prognostic biomarkers, while PET may improve our ability to detect residual disease at critical sites and treatment steps, affecting treatment decisions (Fig. 1). In addition, a new oncogenetic prognostic classifier was identified by the GRAALL-Lysa study (favorable: NOTCH1/FBXW7 mutation and/or no RAS/PTEN mutation/deletion, n = 19; 3-year EFS 95% vs. 46% in unfavorable, n = 30; P = 0.001), with independent prognostic value for EFS, DFS and OS (25).

**Treatment**

**First-line therapy and general patient management**

Current treatment strategies are based on intensive multidrug ALL-type chemotherapy, including CNS prophylaxis, with or without mediastinal radiation therapy (MRT), depending on protocol design and early therapeutic response. Standard lymphoma-like therapy was abandoned because much less effective (2). Therefore, modern LBL protocols include an intensive remission induction chemotherapy, an early CNS prophylaxis, consolidation blocks, and subsequent maintenance therapy. Autologous SCT and allogeneic SCT have been included in some studies and/or evaluated as a better option for patients at high risk of resistance or relapse. The approach does not basically change for patients with limited or advanced disease. The initial management of patients with large mediastinal tumors may be difficult because of the obstruction or compression of airways and big vessels, or the rapid progression of pleuropericardic effusions leading to cardiorespiratory failure. In this case, no delay is acceptable in securing the LBL diagnosis prior to the start of corticosteroids, which can provide an almost immediate relief. Apart from the draining of any effusion causing hemodynamic or respiratory impairment, the prevention of metabolic and renal complications includes the administration of rasburicase to patients at risk of tumor lysis syndrome.

**Modern therapy of LBL in children**

The introduction of ALL-type regimens led to a significant improvement of results, particularly in the pediatric population. In a first North American study, 5-year event-free survival (EFS) was improved from 35% with COMP to 64% with the ALL-type LSA2-L2 regimen (P < 0.001) (53). In the Memorial Hospital study with LSA-L2 (n = 95), very long-term overall survival (OS) and EFS rates were 79% and 75%, respectively (32). Impressive results were reported by the German group with the NHL-BFM 90 regimen in 105 patients with T-LBL. This schedule, consisting of a 8-drug induction without MRT, followed by 8-week consolidation including methotrexate (MTX) 5 g/m^2, an 8-drug intensification (only in stage III–IV patients), plus maintenance and moderate-dose prophylactic cranial irradiation, resulted in a 5-year EFS rate of 90% (30). High cure rates were confirmed by others with BFM-type ALL therapy in B-LBL as well, from a 10-year EFS of 73% in one study (n = 26) (31) to 5-year EFS and OS of 82% and 85%, respectively, in another (n = 53) (18). In the St Jude’s Hospital experience (n = 146), the introduction of ALL-type therapy improved the 5-year EFS from 20% to 83% (34). The results from these and other relevant studies are summarized in Table 3. Of note, MRT was not part of the initial treatment plan in any of these trials, whereas early CNS prophylaxis consisted of repeated intrathecal injections, systemic high-dose chemotherapy with CNS-penetrating agents (MTX, cytarabine) and/or cranial irradiation. High-dose chemotherapy blocks with antimetabolites (MTX, cytarabine) were in part responsible for the therapeutic improvement. With regard to MTX, a randomized trial (57) points to the use of 5 g/m^2 in T-ALL. However, the benefit was not confirmed in T-LBL, and there is also a lack of comparative data with lower doses.

**Modern therapy of LBL in adults**

Encouraging results were obtained with ALL-type regimens in adults. The University of Texas M.D. Anderson Cancer
In summary, with modern intensive adult LBL protocols, the 2003 protocol without MRT (25), results were comparable. The involvement of CNS in LBL ranges from 3% to 15% (2), with higher rates at relapse, particularly in the absence of adequate CNS prophylaxis. Because cranial irradiation yields a high rate of late toxicities, from neurocognitive disturbance to secondary malignancies, the omission of this component of the prophylactic regimen became a definite clinical goal. The BFM group performed a very successful trial omitting/reducing cranial irradiation (12 Gy only in stage III–IV patients), while intensifying systemic high-dose (HD) CNS-directed therapy with MTX 5 g/m², with only one CNS relapse of 105 patients treated (30). Other effective radiation-free protocols were developed by the Children’s Leukemia Group (CLG), obtaining a CNS relapse rate of only 1.8%, even in patients with CNS involvement at diagnosis (14); by the St Jude’s Hospital (NHL 13 regimen), with only 1 CNS relapse of 41 patients (2.4%) (59); and by the Children’s Oncology Group (COG), with no CNS relapse of 60 patients treated in one trial (35) and no difference in 5-year EFS (80–84%) by type of CNS prophylaxis (intrathecal MTX vs. HD-MTX maintenance) or by intensification of intrathecal MTX in another trial, with a cumulative incidence of CNS relapse of only 1.2% (36).

In the adult setting, some retained cranial irradiation (25, 38, 44), while others did not (39, 40, 42). However, CNS relapse rates were consistently low (1.2–3%), suggesting that even in adult patients radiotherapy could be safely omitted when intrathecal prophylaxis is associated with systemic...
<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol/Protocol</th>
<th>Patients</th>
<th>Age</th>
<th>BM Involvement</th>
<th>Treatment</th>
<th>EFS</th>
<th>OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoelzer et al. (37)</td>
<td>GMALL</td>
<td>45</td>
<td>15-61</td>
<td>No</td>
<td>24 Gy</td>
<td>–</td>
<td>93 EFS 26% (7-year)</td>
</tr>
<tr>
<td>Le Gouill et al. (38)</td>
<td>LNH87/LNH93</td>
<td>92</td>
<td>16-69</td>
<td>No</td>
<td>No</td>
<td>Random autologous SCT vs. consolidation In patient aged &lt;55 (lnh87) and &lt;60 (lnh93)</td>
<td>71 EFS 22% (5-year)</td>
</tr>
<tr>
<td>Thomas et al. (39)</td>
<td>Hyper-CVAD</td>
<td>33</td>
<td>17-59</td>
<td>No</td>
<td>30-39 Gy</td>
<td>–</td>
<td>91 EFS 66% (3-year)</td>
</tr>
<tr>
<td>Jabbour et al. (40)</td>
<td>LMT-89</td>
<td>27</td>
<td>15-57</td>
<td>BM involvement</td>
<td>No</td>
<td>Standard option (autologous/allogeneic SCT)</td>
<td>44 EFS 44% (7-year)</td>
</tr>
<tr>
<td>Song et al. (41)</td>
<td>NHL protocol, NHL/ALL hybrid protocol</td>
<td>34 T-LBL</td>
<td>NR</td>
<td>BM involvement</td>
<td>No</td>
<td>–</td>
<td>90 EFS 72% (5-year)</td>
</tr>
<tr>
<td>Cortelazzo et al. (42)</td>
<td>NILG-ALL 09/00</td>
<td>30</td>
<td>16-57</td>
<td>MRD+</td>
<td>24 Gy (if CT+ post-induction)</td>
<td>MRD+ (autologous/allogeneic SCT)</td>
<td>4 EFS 72% (5-year)</td>
</tr>
<tr>
<td>Bersvendsen et al. (43)</td>
<td>ALL-type</td>
<td>25</td>
<td>15-65</td>
<td>No</td>
<td>24-32 Gy</td>
<td>4.5</td>
<td>84.5 EFS 76% (5-year)</td>
</tr>
<tr>
<td>Wang et al. (44)</td>
<td>BFM-90</td>
<td>36</td>
<td>NR</td>
<td>Female gender, hepatomegaly, anemia</td>
<td>No</td>
<td>–</td>
<td>94 EFS 65% (3-year)</td>
</tr>
<tr>
<td>Hocking et al. (54)</td>
<td>FRALLE-93</td>
<td>40</td>
<td>16-45</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>97 EFS 70% (3-year)</td>
</tr>
<tr>
<td>Ellin et al. (3)</td>
<td>ALL-type</td>
<td>30</td>
<td>18-78</td>
<td>CNS+, female gender</td>
<td>21-36 Gy</td>
<td>Unclear criteria (autologous/allogeneic SCT)</td>
<td>57 EFS 49% (5-year)</td>
</tr>
<tr>
<td>Goekbuget et al. (45)</td>
<td>GMALL</td>
<td>149</td>
<td>17-62</td>
<td>–</td>
<td>36 Gy (only cohort 1)</td>
<td>–</td>
<td>76 OS 65% (5-year)</td>
</tr>
<tr>
<td>Lepretre et al. (24)</td>
<td>GRAALL-Lysa LL03</td>
<td>148</td>
<td>18-59</td>
<td>NOTCH1/POX7 mutation and/or no RAS/PTEN mutation/deletion</td>
<td>No</td>
<td>–</td>
<td>91 (T) EFS 63% (3-year)</td>
</tr>
<tr>
<td>Xie et al. (46)</td>
<td>BFM-90</td>
<td>57</td>
<td>14-54</td>
<td>Abnormal WBC, high IPI, no early response</td>
<td>No</td>
<td>Autologous SCT</td>
<td>75 PFS 60% (3-year)</td>
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NR, not reported.

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HD-MTX and cytarabine. A very effective radiation-free prophylaxis combining MTX 5 g/m² with intrathecal liposome-associated cytarabine was recently reported in adult ALL (CNS relapse 0% in T-ALL) (60).

Treatment of mediastinal disease

Mediastinal disease is a frequent site of presentation and one of the most frequent sites of relapse. Although therapeutically very useful, MRT is not indisputably effective, delays chemotherapy, and carries the risk of cardiac and pleuropericardic damage, radiation pneumonia, and secondary malignancies (2), which are of the greatest concern in children and young adults. To avoid this morbidity, MRT has been successfully eliminated from pediatric LBL protocols. In particular, the BFM group adopting the intensive protocol with increased MTX dosing obtained a 90% 5-year EFS with a low rate of mediastinal relapse (7%) (30). Instead, the mediastinal relapse rate was higher in adult LBL GMALL study (7 patients, 6 of whom had MRT), in spite of the intensive chemotherapy (with 1.5 instead of 5 g/m² MTX dosing, prednisone instead of dexamethasone and fewer CNS prophylaxis injections compared with the pediatric BFM trial) associated with 24 Gy MRT (38). To improve, a new GMALL protocol increased the radiation dose (36 Gy), by which the risk of mediastinal recurrence was minimally reduced compared with no MRT at all (17% vs. 24%) (44). Also in the MDACC experience some patients relapsed in the mediastinum, in spite of MRT (30–39 Gy) given at the end of Hyper-CVAD (39). In the NILG study, in which MRT was prescribed only to patients with postinduction residual mediastinal mass, a mediastinal recurrence occurred in only 1 of 14 non-irradiated patients (7%), suggesting the value of a selective MRT guided by the early CT results (42). In other studies without MRT but including modern high-dose chemotherapy blocks similar to pediatric ALL regimens, the rate of mediastinal relapse was similarly low to very low (25, 40). Altogether, the routine use of MRT in LBL does not appear necessary and would ideally be based on clear data supporting its success.

The management of a residual mediastinum is another controversial issue. In the pediatric setting a biopsy performed in 10 patients with T-LBL found only necrotic tissue (30). Although PET reevaluation can help define which patients need supplemental therapy, including MRT, the two recent studies from GMALL (44) and GRAALL-Lysa (25) suggest that chemotherapy should not be deferred, and provided that a clinical CR/CRu is achieved after consolidation I (GMALL) or after induction/salvage (GRAALL-Lysa), the risk of failure due to mediastinal progression is low and is not predicted by PET results (GRAALL-Lysa), although a negative PET scan is confirmatory of CR/CRu (GMALL), and is not significantly modified by additional MRT (GMALL). Clearly, a most difficult issue is to identify those patients for whom MRT is necessary to prevent a mediastinal recurrence.

Stem cell transplantation

Autologous SCT

In the past, very HD chemotherapy and autologous SCT or, to a lesser extent, SCT have been used as final consolidation
therapy in several studies (2). The impact of autologous SCT on DFS ranged from 31% to 77% for patients in CR1, accounting for 43–50% of long survivors after chemosensitive relapse. However, SCT results are affected by a selection bias (61). A small randomized trial showed a trend for improved relapse-free survival with autologous SCT compared with chemotherapy (55% vs. 24%), but the chemotherapy schedule in this study could be suboptimal by today’s standards (62). More recent studies on SCT reported higher OS/EFS rates of 72–84% and 68–76%, respectively (41, 43, 63), but again these results are not better than those obtainable with modern intensified ALL-type regimens and there was no difference between autologous and allogeneic SCT. In the NILG study, adopting a risk-adapted strategy with autologous/allogeneic SCT reserved to poor responders and/or MRD+ patients (Fig. 1), there were 14 SCTs (11 autologous), with DFS and OS estimates of 77% and 72%, respectively (42).

**Allogeneic SCT**

With regard to allogeneic SCT, some studies qualified high-risk patients for the procedure (25, 42, 64). Despite the negative patient selection, the results were encouraging, with a DFS ranging from 59% to 91% in CR1, but only 16% in advanced disease. A wide multicenter retrospective study on 76 allografted patients showed fewer relapses with autologous than autologous SCT (34% vs. 56%; \( P = 0.004 \)) but higher transplant-related mortality (18% vs. 3% at 6 months; \( P = 0.002 \)) which offset the potential therapeutic benefit (65). Similar data were provided by others (66). In the GRAALL-Lysa study, the allogeneic SCT was offered to patients with high-risk disease defined by CNS+ status or need of salvage chemotherapy to achieve CR/Cru (25). Seventeen patients had an allogeneic SCT, with an outcome similar to non-SCT patients. Again, these results suggest that an allogeneic SCT may be effective in patients with high-risk features and/or suboptimal response to standard induction/consolidation therapy.

**Treatment of relapsed/refractory LBL**

**Salvage chemotherapy**

The management of relapsed/refractory (r/r) LBL is difficult and follows the same principles of r/r ALL, with only minor differences (i.e., the possibility of adding radiation therapy to localized involved sites). The general therapeutic strategy is to induce a new remission followed by an allogeneic/autologous SCT (2), a design which often fails due to the rapid progression of disease, treatment toxicities, and lack of suitable HLA-matched donors and/or problems affecting SCT logistics. Salvage with drugs used in front-line therapy leads to dismal result. The SMILE regimen (dexamethasone, methotrexate, ifosfamide, L-asparaginase, and etoposide) was used in 11 r/r LBLs, yielding three CRs and 4 partial responses (67). Although in some pediatric r/r LBL studies the probability of survival was 25–50% (68, 69), in the German BFM study in which only 10% of the patients suffered from resistance or relapse the salvage rate was extremely poor (OS 14%), and a long-term survival was only achieved in the few patients having an allogeneic SCT (70). Results are certainly worse in adults. In the GMALL series, only one of 15 r/r patients with T-LBL survived long term (38).

**New drugs**

An interesting drug for r/r T-LBL is nelarabine, a pro-drug that is demethylated to deoxyguanosine and has significant activity as single agent in r/r T-ALL. However in a GMALL trial, none of 19 patients with r/r T-LBL entered CR as opposed to 45/107 (45%) with T-ALL (\( P = 0.0004 \)), while in the smaller CALGB study the CR rate was 31% (4/13 T-LBLs) (71, 72). With a combination of nelarabine, etoposide, and cyclophosphamide, 2 pediatric patients with r/r LBL had a partial response in one study (73) and three of 5 obtained a CR in another (74). This drug is also evaluated as first-line drug in combination regimens. A recent pediatric study by COG confirmed the safety of nelarabine in association with intensive chemotherapy in T-ALL (75). Efficacy results from a phase III trial are awaited with interest. Combination chemotherapy including nelarabine was adopted in 23 and 17 adult patients with untreated T-ALL and T-LBL, yielding cumulative 3-year OS and DFS rates of 63% and 61%, respectively, with a trend to better results in T-LBL (76).

Clofarabine is a second-generation purine nucleoside analog, which has been used in salvage regimens for r/r ALL, especially in the pediatric setting, leading to CR in 30–60% of the cases with an acceptable tolerability profile. However, activity in r/r T-ALL is lower than for B-lineage ALL, even in combination with cyclophosphamide, etoposide, and other drugs. The reported CR rates in T-ALL/LBL were 11% (1/9), 12.5% (1/8), and 50% (2/4) (77–79). Forodesine is an orally bioavailable purine nucleoside phosphorylase inhibitor, deserving evaluation in T-LBL. Another potentially useful agent is bortezomib, the proteasome inhibitor tested with some success in B-lineage ALL (80) and under evaluation in a COG randomized trial.

**New targeted therapy**

**Experimental drugs**

Several new agents hold promise for an improved management of r/r ALL and LBL as well. However, the most exciting innovations represented by cytotoxic monoclonal antibodies (rituximab, inotuzumab ozogamicin,
blinatumomab) and chimeric antigen receptor-modified T cells (CD19.CAR T) (81), highly active in B-cell ALL, cannot be exploited in the great majority of patients with LBL, 90% of whom have a T-cell disease. The anti-CD20 monoclonal antibody rituximab could be used in B-LBL, which is rare and frequently CD20-negative (12/35 CD20+ in one study, i.e., 34%) (28). Because of that and the limited access to experimental therapy with CAR T cells, inotuzumab and blinatumomab, these items will not be further discussed.

**Therapeutic monoclonal antibodies for T-LBL**

The pan-lymphocyte antigen CD52 is widely expressed by B- and T-cell malignancies and is targeted by the monoclonal antibody alemtuzumab. Alemtuzumab was used to treat a variety of hematopoietic tumors, showing limited activity in ALL (8% CR rate, 0% in T-ALL [0/3]) (82) and significant toxicity (83). The drug is now hardly available. Of greater interest is the anti-CD30 monoclonal antibody brentuximab vedotin, in relation to the CD30 antigen expression reported in 38% of 34 T-ALL cases (84). Highly effective in r/r CD30+ lymphomas, brentuximab is a serious candidate to implement the concept of immunotherapy in r/r T-LBL.

**Small inhibitors for T-LBL**

Among several potentially active molecules, NOTCH1 inhibitors are the most interesting ones because of the central pathogenetic role of activating NOTCH1 mutations in T-ALL/LBL. Gamma secretase inhibitors (GSI), blocking NOTCH1 activation, can exert therapeutic activity, with an associated gastro-intestinal toxicity that is mitigated by dexamethasone. In a recent phase I trial (85), eight of 25 adult patients with r/r T-ALL/LBL treated with the BMS-906024 GSI had at least a 50% reduction in bone marrow blast cells (all with T-ALL), and one CR was recorded. This represents a new promising avenue of therapeutic research in T-LBL.

**Conclusions**

LBL is a rare disease, biologically close to but clinically and prognostically distinct from ALL, and with a better overall prognosis. The modern management of LBL follows the same principles of ALL therapy. Considering the very bad outlook of r/r disease and taking into account the outstanding 90% EFS rate obtained in a large BFM pediatric series (30), comparable regimens should be adopted in all patients regardless of age. It is worth noting how 5 g/m² MTX blocks were part of this highly effective schedule, in which MRT was safely omitted and low-dose cranial irradiation was delivered only to patients with advanced disease. In this context, neither allogeneic SCT nor autologous SCT are necessary, unless indicated by an adverse course of the disease and/or specific high-risk situations, and preferably within a prospective clinical trial. Finally, looking for more robust prognostic indicators, the presence of adverse (onco)-genetic abnormalities and the early evaluation of CT/PET and MDD/MRD response should allow a more rational, risk-oriented use of MRT, SCT, and new targeted therapies.

**Conflict of interest and sources of funding statement**

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Lymphoblastic lymphoma


