Current status and future directions of T-lymphoblastic lymphoma in children and adolescents

Birgit Burkhardt,1 Stephanie Mueller,1 Tasneem Khanam1 and Sherrie L. Perkins2

1Paediatric Haematology and Oncology, University Hospital Muenster, Germany and 2Department of Pathology, University of Utah Health Sciences Center, ARUP Institute for Clinical and Experimental Pathology, Salt Lake City, Utah

Summary

The main challenges in the treatment of T-cell lymphoblastic lymphoma (T-LBL) in children and adolescents are twofold: to increase survival rates in concert with reduction of acute and long-term toxicities including the rate of secondary malignancies. The need for molecular and prognostic markers in T-LBL is crucial to allow for systematic treatment optimization and may serve as targets for new treatment approaches.

Keywords: Paediatric T-lymphoblastic lymphoma, molecular markers, risk group stratification, genetic classifier, treatment.

T-cell lymphoblastic lymphoma (T-LBL) is the second most common subtype of Non-Hodgkin lymphoma (NHL) in children and adolescents. Both T-LBL and acute T-cell lymphoblastic leukaemia (T-ALL) represent T-cell progenitor malignancies, that share overlapping clinical, morphological and immunophenotypic features but differ by the extent of bone marrow infiltration (<25% in lymphoma compared to ≥25% in leukaemia). Although event-free survival probabilities (pEFS) have improved (75–85% with current ALL-type chemotherapy protocols) (Patte et al., 1992; Tubergen et al., 1995; Amylon et al., 1999; Reiter et al., 2000, 2012; Burkhardt et al., 2006a; Abromowitch et al., 2008; Yttebroeck et al., 2008, 2012; Pillon et al., 2009, 2015; Sandlund et al., 2009; Asselin et al., 2011; Termuhlen et al., 2012, 2013; Gao et al., 2014; Bergeron et al., 2015; Sunami et al., 2015), there are still dismal outcomes for those who relapse, with survival rates of 10–30% (Burkhardt et al., 2009; Mitsui et al., 2009; Gross et al., 2010). Furthermore, relevant treatment-associated mortality and toxicities, late effects and the elevated risk of secondary malignancies are critical aspects in treating paediatric patients with T-LBL, indicating an urgent need for identification of prognostic markers to allow early risk group stratification and design of risk-adjusted treatment protocols, as schematically outlined in Fig 1. While there is some overlap in the molecular genetics of paediatric T-ALL and T-LBL, the established T-ALL risk group stratification cannot be extrapolated to paediatric T-LBL patients (Burkhardt, 2010; Basso et al., 2011).

T-LBL epidemiology

The overall incidence of T-LBL appears relatively constant across most paediatric age groups, decreasing in adolescents and young adults (incidence rate of 0.4/100,000 in children <15 years of age and 0.1/100,000 in adolescents and young adults) (Burkhardt et al., 2005; Geyer & Jacobson, 2012). T-LBL occurs more commonly in males and is more frequent in whites in the United States (Altekruse et al., 2010). There are distinct geographical variations in incidence, with T-LBL representing approximately 15–25% of paediatric and adolescent NHL in Europe and the United States, with lower relative incidences in equatorial Africa, probably reflecting the relative increase in Burkitt lymphoma cases associated with human immunodeficiency virus and Epstein–Barr virus infection (Mbulaiteye et al., 2003; Sitas et al., 2008). The incidence of T-LBL in children and adolescents is higher in Asia than in Europe and the United States, and in Asia T-LBL represents the most frequent subtype of paediatric NHL (Shih & Liang, 1991). The overall incidence of T-LBL in most studies comprises 1–4% of all NHL in both Western and Asian populations, with the notable exception of India, which appears to have an incidence that is slightly higher than in other countries (6–7%) although much of the published data does not stratify by age and represents limited data set analysis (Shih & Liang, 1991; Naresh et al., 2000, 2004; Muller et al., 2005). No specific aetiological associations have been identified for the majority of T-LBL in children and adolescents.
However, for a minority of cases with underlying disease characterized by chromosomal instability or DNA repair deficiencies, there is growing evidence for an increased risk of T-LBL (Bienemann et al, 2011; Wimmer et al, 2014).

**Patient characteristics**

The median age at presentation of paediatric T-LBL patients (summarized in Table I) ranges from 7 years (Children’s Oncology Group [COG] A5971 trial) (Termuhlen et al, 2012) to 10.5 years (Bergeron et al, 2015). The male:female ratio for a population-based NHL Berlin-Frankfurt-Munster (BFM) cohort in Europe was 2:5:1, with a significantly superior outcome for males. At diagnosis, 97% of patients presented with stage III or IV (77% and 20%, respectively) disease (Burkhardt et al, 2005). A mediastinal mass was reported for most patients, often accompanied by pleural or pericardial effusions. Interestingly, in a Chinese cohort of 108 LBL patients including 85% T-LBL, only 52% of patients presented with a mediastinal mass (Gao et al, 2014). In the European Organization for Research and Treatment of Cancer (EORTC) trial 58881, 80% of 119 analysed T-LBL patients presented with mediastinal masses (Uyttebroeck et al, 2008). These differences might be, at least partly, explained by the imaging methods used. Infiltration of peripheral lymph nodes is common in T-LBL, and bone marrow involvement occurs in 15–20% of patients (Burkhardt et al, 2005; Abromowitch et al, 2008). Central nervous system (CNS) involvement is infrequent, with <5% of analysed patients affected (Burkhardt et al, 2005; Abromowitch et al, 2008; Uyttebroeck et al, 2008). To date, none of these clinical parameters could be confirmed independently as being of prognostic relevance amongst international clinical trials (Fig 1).

**Pathology and staging**

The initial diagnostic workup for patients with T-LBL requires histological and immunohistochemical evaluation and these studies may be performed on tissue lymphoma or malignant cells in fluids (e.g. pleural effusions). For difficult cases, or as needed, central reference laboratories may be consulted to avoid misdiagnosis (Oschlies et al, 2011; Minard-Colin et al, 2015). The pathological features of T-LBL are characterized by diffuse or partial (cortical expansion) effacement of nodes by T-lymphoblasts that are cytologically similar to those seen in T-ALL. The blasts are intermediate in size with fine chromatin, variable nuclear convolutions and nucleoli and variable amounts of agranular cytoplasm. Usually the neoplastic cells have scanty cytoplasm and mitotic figures may be frequent. The immunophenotype is heterogeneous but usually reflects T-cell lineage with variable expression of T-cell antigens including CD2, CD4, CD5, CD7 and CD8. CD3 is often expressed in the cytoplasm but is not present on the cell surface. The most commonly expressed T-cell antigens are CD2, CD5 and CD7. Markers of blastic differentiation, such as CD1a, CD34 and TdT are usually present. CD10 is seen in approximately half of cases. Cell surface antigen expression will approximate the level of T-cell differentiation with pro-thymocyte and pre-thymocyte stages lacking expression of CD4 and CD8, whereas the more frequently seen cortical thymocyte stage will have co-expression of CD4 and CD8. Tumours with a medullary stage of differentiation will lack prognostically significant recurrent cytogenetic abnormalities, as described in precursor B-ALL (Swerdlow et al, 2008). Studies have identified different gene expression profiles and genetic signatures when comparing T-LBL and...
Table I. Recent clinical trials for paediatric patients with LBL emphasizing stage, patient number, treatment regimen, outcome, events, second malignancy, CNS therapy and pEFS.

<table>
<thead>
<tr>
<th>Trial/reference</th>
<th>Median Age (years)</th>
<th>Stage</th>
<th>Patients (T-LBL), n</th>
<th>Treatment</th>
<th>Relapse (CNS-involvement)/Progression</th>
<th>Events/SMN</th>
<th>CNS therapy</th>
<th>pEFS</th>
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<tbody>
<tr>
<td>LMT81 Patte et al (1992)</td>
<td>9</td>
<td>I-IV</td>
<td>84</td>
<td>Modified LSA2-L2 (+10 courses of HD-MTX)</td>
<td>13 (2) relapses, stage III, IV</td>
<td>Toxic deaths stage II, III, one severe pancreatitis</td>
<td>CR 24 Gy, IT-triple therapy</td>
<td>75 ± 3% (overall)</td>
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<tr>
<td>CGG502 Tubergen et al (1995)</td>
<td>9</td>
<td>I-IV</td>
<td>143 (a) 138 (b)</td>
<td>Randomization modified LSA2-L2 (a) vs ADCOMP (b)</td>
<td>81 (8) relapses 4/28, stage I, II 63/206: mediastinal primary tumour</td>
<td>3 deaths due to treatment toxicity, 3 cases of AML, 81 events related to PD</td>
<td>2 x additional IT-MTX, CR (24 Gy) and spinal irradiation (12 Gy)</td>
<td>74% (a)/ 64% (b)</td>
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<tr>
<td>POG 8704 Amylon et al (1999)</td>
<td>10</td>
<td>III/IV</td>
<td>83 (a) 84 (b) (all T-LBL)</td>
<td>Local institution and POG protocol with randomization L-Asp - (a) vs. L-Asp + (b)</td>
<td>31 (2) relapses (a), 17 (4) relapses (b)</td>
<td>8 SMN (non-lymphocytic leukaemia, MDS), 1 fatal leucoencephalopathy, 2 deaths in complete remission</td>
<td>CR plus 2 additional IT-triple therapy</td>
<td>64 ± 6% (a) 78 ± 5% (b)</td>
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<tr>
<td>NHL BFM90 Reiter et al (2000)</td>
<td>9</td>
<td>I-IV</td>
<td>105 (T-LBL)</td>
<td>ALL-BFM-type treatment</td>
<td>8 (1) relapses, stage III/IV, all died</td>
<td>1 secondary AML, 1 early death, no toxic death, 8 tumour failures</td>
<td>2 additional IT-MTX (induction) plus CR 18 Gy (second year of life), ≥2 years: 24 Gy</td>
<td>90% (overall) 90 ± 3% (III) 95 ± 5% (IV)</td>
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<tr>
<td>NHL BFM95 Burkhardt et al (2006a)</td>
<td>8</td>
<td>III/IV</td>
<td>169 (126)</td>
<td>Modified NHL BFM 90</td>
<td>18 (3) tumour failures</td>
<td>2 toxic deaths, 3 early deaths, 5 SMN (AML)</td>
<td>2 additional IT-MTX (induction) plus CR 12 Gy (second year of life), ≥2 years: 18 Gy</td>
<td>78 ± 3% T-LBL: 80 ± 4%</td>
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<tr>
<td>EORTC 58881 Uyttebroeck et al (2008)</td>
<td>8</td>
<td>I-IV</td>
<td>119 (T-LBL)</td>
<td>NHL BFM-type therapy, no CR</td>
<td>18 (3) relapses, of whom 10 died</td>
<td>1 death due to infectious complication, 1 SMN (AML)</td>
<td>Additional IT-MTX during induction up until normalization of CSF, 5 courses of IT-MTX plus 3 courses of HD-MTX</td>
<td>78 ± 3% (overall) 86 ± 13% (I) 64 ± 21% (II) 78 ± 5% (III) 77 ± 8% (IV)</td>
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<tr>
<td>COG pilot Abromowitch et al (2008)</td>
<td>n.d.</td>
<td>III/IV</td>
<td>85 (77)</td>
<td>Modified LSA2-L2</td>
<td>13 (2) relapses</td>
<td>2 SMN (AML), 4 toxic deaths, 1 death due to VOD</td>
<td>Additional HD-Ara-C and HD-MTX, increased number of IT-therapy, CR</td>
<td>78 ± 5%</td>
</tr>
<tr>
<td>LNH92 Pillon et al (2009)</td>
<td>8</td>
<td>I-IV</td>
<td>55 (47)</td>
<td>Modified LSA2-L2</td>
<td>13 (0) (12 T-LBL) relapses, of whom 11 died (all stage III/IV)</td>
<td>No toxic death, no SMN, 5 cases of neurological toxicity, 1 death due to second-look surgery</td>
<td>Additional HD-Ara-C and HD-MTX, increased number of IT-therapy, CR</td>
<td>69 ± 6% (overall) 100% (I, II) 62% (III) 75% (IV)</td>
</tr>
<tr>
<td>Trial/reference</td>
<td>Median Age (years)</td>
<td>Stage (T-LBL), n</td>
<td>Treatment</td>
<td>Relapse (CNS-involvement)/Progression</td>
<td>Events/SMN</td>
<td>CNS therapy (CNS+ patients)</td>
<td>pEFS</td>
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<td>St Jude NHL 13 Sandlund et al (2009)</td>
<td>n.d.</td>
<td>III/IV</td>
<td>41 (33)</td>
<td>T-ALL-like therapy</td>
<td>3 (1) relapses, 2 induction failures</td>
<td>1 secondary AML, 1 death due to infectious complications</td>
<td>7 additional courses of IT-triple therapy</td>
<td>83 ± 6%</td>
</tr>
<tr>
<td>POG 9404 Asselin et al (2011)</td>
<td>50% aged &lt;10</td>
<td>III/IV</td>
<td>71 (a), 66 (b) all T-LBL</td>
<td>Modified DFCI (Dana-Faber Leukemia Consortium) ALL with (a) or without (b) HD-MTX</td>
<td>10 (2) relapses (a), 5 (1) relapses (b)</td>
<td>3 SMN (astrocytoma, myeloid sarcoma, papillary carcinoma), total of 23 failures, 3 remission deaths</td>
<td>2 additional courses of IT-triple therapy, CR for all patients</td>
<td>82 ± 5% (a), 80 ± 6% (III), 88 ± 7% (IV), 88 ± 4% (b), 88 ± 5% (III), 87 ± 7% (IV)</td>
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<tr>
<td>A 5971 Termuhlen et al (2012)</td>
<td>7</td>
<td>I/II</td>
<td>56 (8)</td>
<td>CGG BFM</td>
<td>5 (0) relapses, of whom 4 died, 1 LFU</td>
<td>No toxic deaths, osteonecrosis in 2 cases, 2 SMN (Ewing, AML)</td>
<td>Prophylaxis: no IT-MTX on day 28 during maintenance</td>
<td>90% (T-LBL: 100%)</td>
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<td>EURO-LB02 Reiter et al (2012)</td>
<td>I–IV</td>
<td>319 (233), 98 (a), T–LBL 88 (b), T–LBL</td>
<td>BFM, randomization Dex (10 mg/m²) (a) vs Pred (60 mg/m²) (b)</td>
<td>42 (9, Pred) tumour failures: 10 (a); 13 (b)</td>
<td>All: 12 toxic deaths, 5 SMN</td>
<td>According to NHL BFM90</td>
<td>81 ± 2% (overall), 84 ± 4% (a), 84 ± 4% (b)</td>
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<tr>
<td>EORTC 58951 Uyttebroeck et al (2012)</td>
<td>I–IV</td>
<td>all T-LBL: 37 (a) 37 (b)</td>
<td>Modified BFM, randomization Dex (6 mg/m²) (a) vs Pred (60 mg/m²) (b)</td>
<td>5 (1) relapses: 1 (a); 4 (b)</td>
<td>4 deaths in complete remission (a)</td>
<td>Prophylaxis: 6 IT induction-consolidation + late intensification, 4x HD-MTX + IT, additional 6 x HD-MTX + IT maintenance</td>
<td>85% (overall), 81% (a), 89% (b)</td>
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<tr>
<td>COG A5971 Termuhlen et al (2013)</td>
<td>10</td>
<td>III/IV</td>
<td>257 (191)</td>
<td>Modified NHL BFM, randomization HD-MTX (a) vs intensified IT-MTX (b)+ intensification (c) vs without intensification (d)</td>
<td>30 (3) relapses, 9 progressions</td>
<td>5 SMN (2 AML, malignant histiocytic sarcoma, mucoepidermoid carcinoma), 36 deaths (4 deaths related to therapy), 10 cases of osteonecrosis</td>
<td>Therapy according to (a), (c) and NHL BFM 95</td>
<td>84% (a, d), 81% (b, d), 80% (a, c), 80% (b, c)</td>
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### Table 1 (Continued)

<table>
<thead>
<tr>
<th>Trial/reference</th>
<th>Median Age (years)</th>
<th>Stage</th>
<th>Patients (T-LBL), n</th>
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<th>Relapse (CNS-involvement)/Progression</th>
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<th>CNS therapy (CNS+ patients)</th>
<th>pEFS</th>
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<tr>
<td>CCCG-99/SCMC-T-NHL-2002/LBL-CHOF-2006 Gao et al (2014)</td>
<td>7-9</td>
<td>I-IV</td>
<td>108 (92)</td>
<td>CHOP/COMP-like (CCCG-99) (a), local institution protocol (SCMC) (b), modified NHL BFM90 (CHOF) (c)</td>
<td>25 (2) relapses/PD of whom 22 died, all T-LBL</td>
<td>4 treatment-related deaths, no SMN</td>
<td>CR (18 Gy) &gt; 2 years, additional triple therapy or IT-MTX</td>
<td>56 ± 10% (a)</td>
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<td>63 ± 7% (b)</td>
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<td>69 ± 8% (c)</td>
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<td>71 ± 17% (I, II)</td>
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<td>67 ± 5% (III, IV)</td>
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<td>LNH97 Pillon et al (2015)</td>
<td>9</td>
<td>I–IV</td>
<td>114 (88)</td>
<td>Modified LSA2-L2-derived LNH92</td>
<td>25 (2) relapses, of whom 18 died, 21/25 T-LBL, 2 failures due to PD</td>
<td>No toxic death, 2 SMN (AML, thyroid carcinoma)</td>
<td>HD-Ara-C during consolidation, additional IT therapy, CR 18 Gy (second year of life), &gt;2 years: 24 Gy</td>
<td>74 ± 4% (overall, 7 years)</td>
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<td>82 ± 12% (I, II)</td>
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<td>74 ± 5% (III)</td>
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<td>72 ± 8% (IV)</td>
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<td>SFOP LMT96 Bergeron et al (2015)</td>
<td>10-5</td>
<td>I–IV</td>
<td>79 (T-LBL)</td>
<td>Modified NHL BFM</td>
<td>9 (1) relapses, of whom 8 died, 1 initial progression</td>
<td>3 SMN (1 glioblastoma, 1 AML, 1 thyroid carcinoma), 11 deaths (8 relapses, 1 early PD, 2/3 SMN)</td>
<td>IT triple therapy, CR (18 Gy) down to C2 vertebra after 3 monthly pulses intensified with asparaginase and MTX</td>
<td>85%</td>
</tr>
<tr>
<td>ALB-NHL03 Sunami et al (2015)</td>
<td>9</td>
<td>III/IV</td>
<td>136 (104)</td>
<td>Modified NHL BFM</td>
<td>15 (2) relapses, of whom 12 died</td>
<td>30 events (including relapses): 22 died, 1 toxic death, 1 SMN (colon cancer)</td>
<td>2 additional IT-MTX (induction) plus CR 12 Gy (second year of life), &gt;2 years: 18 Gy</td>
<td>77 ± 4% (T-LBL)</td>
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<td>70-6% (III)</td>
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<td>88-9% (IV)</td>
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T-LBL: T-cell lymphoblastic lymphoma; CNS: central nervous system; SMN: secondary malignancies; pEFS: probability of event-free survival; n.d.: not determined; Ara-C: cytarabine; MTX: methotrexate; IT: intrathecal; triple therapy: intrathecal therapy with hydrocortisone, Ara-C, MTX; ADCOMP: daunorubicin, asparaginase, MTX, cyclophosphamide, vin-cristine, prednisone; Dex: dexamethasone; Pred: prednisolone; L-asp: L-asparaginase; CR: cranial irradiation; HD: high dose; LFU: lost to follow up; PD: progressive disease; VOD: veno-occulsive disease; ALL: acute lymphoblastic leukaemia; AML: acute myeloid leukaemia; MDS: myelodysplasia.
T-ALL, suggesting that there may be underlying biological and genetic differences between these entities despite their similar immunophenotypes and morphological features (Raetz et al, 2006; Burkhardt, 2010).

Recently it has been recognized that a very early stage of differentiation may be seen in about 10–15% of cases of T-ALL, termed early T-precursor acute lymphoblastic leukaemia (ETP-ALL), defined as having expression of T-cell antigens CD7 and low level CD5 (and occasionally cytoplasmic CD3), but lacking expression of CD1a, CD4 and CD8. There is expression of CD34 as well as at least one myeloid-related antigen, such as CD117, CD33 or CD13 (Coustan-Smith et al, 2009a; You et al, 2015) and has also been described in T-LBL (Patel et al, 2012). This phenotype is associated with increased acute myeloid leukaemia-type mutations rather than T-ALL/LBL-associated NOTCH mutations (Haydu & Ferrando, 2013). ETP-ALL was originally described as higher risk disease due to increased induction failures, but more recent data does not show significant differences in outcomes with current therapies (Patrick et al, 2014). On-going analyses of histological and immunophenotypic characteristics of T-LBL could complement the current criteria to identify biological T-LBL subgroups with distinct chemosensitivity (Fig 1).

Staging of newly diagnosed patients includes complete medical history, physical examination and lumbar puncture with cerebrospinal fluid (CSF) cytology, bone marrow aspirate and, possibly, bone marrow biopsy. Laboratory tests should include a full and differential blood count, assessment of kidney and liver function, electrolytes and lactate dehydrogenase level. Imaging procedures include abdominal ultrasound and ultrasound of lymph nodes as well as testicular ultrasound in case of male patients. Imaging procedures may be extended with magnetic resonance imaging (MRI) or computerized tomodraphy (CT). Fluorodeoxyglucose (FDG) positron emission tomodraphy (PET)/CT scanning is now more frequently used for routine staging in T-LBL patients, but published data is limited (Riad et al, 2010a,b; Nakatani et al, 2012; Sioka, 2013; Bardi et al, 2014) and the role of FDG-PET-CT in the management remains to be evaluated.

To date, the St. Jude NHL staging classification has been applied to paediatric patients with NHL (Murphy, 1980). Recently, a revised classification system, the International Paediatric Non-Hodgkin Lymphoma Staging System (IPNHLLSS), which allows more precise documentation of extra-nodal dissemination and advanced diagnostic and imaging methods has been introduced (Rosenol et al, 2015). For standardized response evaluation, the recently published International Paediatric Non-Hodgkin-Lymphoma Response Criteria (Sandlund et al, 2015) includes the use of more sensitive imaging and pathological techniques (e.g. FDG-PET-CT imaging, molecular and immunophenotypic analyses).

Minimal disseminated disease (MDD) and minimal residual disease (MRD)

Risk-stratification in T-ALL is primarily based on microscopic and submicroscopic evaluation of blasts in the peripheral blood and bone marrow using either quantitative PCR based patient-specific T cell receptor gene rearrangements or flow cytometric analysis. Both methods were extended to paediatric T-LBL samples for MDD evaluation (Coustan-Smith et al, 2009b; Stark et al, 2009). Coustan-Smith et al (2009b) revealed that flow cytometric analysis of blood samples provided sensitive detection of disseminated T-LBL, allowing for screening of blast clearance during therapy. Their analysis predicted inferior outcomes for stage IV disease and could distinguish patients with disease dissemination amongst the stage II/III disease, suggesting systemic disease dissemination could play a role in risk stratification. Prospective trials are needed to evaluate the role of MDD and MRD evaluation in paediatric T-LBL as prognostic markers.

Molecular genetics

Currently there is a lack of in-depth knowledge about the molecular genetics of paediatric T-LBL due to the rarity of the disease and limited materials for assessment. Comparative studies with limited numbers of cases of T-ALL and T-LBL wherein genomic data and/or gene expression profiles were compared, revealed that, despite having some genetic similarities, these two manifestations of precursor T-cell malignancy may reflect distinct biological entities (Raetz et al, 2006). Furthermore, genetic studies have identified potential novel (PAPPA, NIFL3 and ZNF91) and known candidate genes (NOTCH1, PHF6, MUC4 and PRDM2) with pathogenic relevance in T-LBL (Bonn et al, 2014).

Loss of heterozygosity on chromosome 6q (LOH6q)

Chromosome 6q deletions have been reported in several haematological malignancies indicating poor prognosis (Mancini et al, 2002; Foroni et al, 2003), or without conclusive prognostic relevance (Heerema et al, 2000). LOH6q has been reported to be associated with an unfavourable outcome in T-LBL (Burkhardt et al, 2006b, 2008; Bonn et al, 2013). Paediatric T-ALL and T-LBL patients (127 and 108 patients, respectively) showed clear prognostic differences with respect to LOH6q because the localization of the common minimal LOH regions do not overlap and because LOH6q is not associated with increased risk of relapse in T-ALL (Bonn et al, 2008).

NOTCH1/FBXW7 mutations (N/Fmut)

Mutations in the hot spots of NOTCH1 and FBXW7 are prevalent in tumours (O’Neil et al, 2007). NOTCH1 is a type
I single-pass integral transmembrane protein with extracellular domains comprising of up to 36 tandem EGF-like repeats that mediate ligand binding and an intracellular domain linked via a heterodimerization unit. Activation of canonical NOTCH1 requires the interaction of NOTCH1 receptor with ligands of the Delta/Serrate/Lag2 (DSL) family (including Delta and the Lagged) followed by proteolytic cleavage and release of the active intracellular (ICN1) domain, which is translocated to the nucleus to activate target gene transcription. The NOTCH1 signalling pathway is evolutionarily conserved and plays a vital role in regulation of cell proliferation, normal development of T-lymphocytes, apoptosis, as well as cell fate decisions throughout embryonic development and adult life (Aifantis et al., 2008). Dysregulation of NOTCH1 signalling, usually resulting in hyperactivation, confers a proliferative advantage for the tumour cells in several cancers and also causes developmental defects. FBXW7 belongs to the F-box protein family and is a subunit of the SCF-type E3 ubiquitin ligase complex involved in ubiquitination and subsequent degradation of target genes, including transcription factors and oncogenes like NOTCH1. Mutations in FBXW7 lead to loss of recognition of NOTCH1 and inhibit degradation of activated NOTCH1, resulting in hyperactivation (O’Neill et al., 2007). FBXW7 is involved in cell proliferation, apoptosis, cell cycle and differentiation. The prognostic significance of NOTCH1/FBXW7 mutations in T-ALL patients varies in different recent reports and may depend on the treatment given (Breit et al., 2006; Clappier et al., 2010; Kox et al., 2010; Zaurbier et al., 2010). Little data exists regarding the clinical impact of NOTCH1 mutations in T-LBL. Studies on NOTCH1 and/or FBXW7 mutations with low patient numbers did not reveal a prognostic impact (Baleydier et al., 2008; Park et al., 2009; Clappier et al., 2010). However, a study on 54 uniformly treated French paediatric patients with T-LBL showed significantly better EFS and overall survival (OS) rates in patients with NOTCH1/FBXW7 mutations (N/Fmut) (Callens et al., 2012). Another large cohort of 241 analysed paediatric T-LBL patients uniformly treated according to the same BFM-type protocol confirmed that N/Fmut were associated with a favourable prognosis (Bonn et al., 2013).

CASP8AP2 (FLASH) deletions and absence of biallelic T-cell receptor gamma (TRG) deletions (ABD)

T-LBL patients with absence of biallelic TRG deletion (ABD) and monallelic CASP8AP2 deletion showed a tendency towards poor outcome without statistical significance (Callens et al., 2012). CASP8AP2 (also termed FLASH) protein is a component of Fas-caspase-8 apoptotic pathway and is involved in glucocorticoid signalling (Kino & Chrousos, 2003; Jun et al., 2005). Interestingly, lower expression of CASP8AP2 was a strong predictor of ALL relapse (Flotho et al., 2006). The absence of biallelic TRG deletion is a predictor of poor response to induction chemotherapy and inferior OS in paediatric T-ALL (Yang et al., 2012), but requires a larger cohort of patient samples to establish them as prognostically relevant genetic markers for T-LBL.

PTEN mutations

Phosphatase and tensin homolog on chromosome 10 (PTEN) is a potent tumour suppressor gene and a negative regulator of the class I phosphoinositide-3-kinases (PI3Ks) (Ye et al., 2012). The effect of PTEN inactivation alone and in combination with NOTCH1 mutation has been analysed in 301 children with T-ALL. PTEN inactivation alone was significantly associated with poor prognosis, whereas patients with co-occurring inactivating PTEN mutation and activating NOTCH1 mutations showed excellent long term prognosis (Bandapalli et al., 2013). Similar observations were seen in T-LBL, where inactivating PTEN mutations were associated with inferior outcome and favourable marker NOTCH1 mutations antagonized the unfavourable prognostic effects of PTEN (Balbach et al., 2015). Furthermore, PTEN mutated and LOH6q positive patients had an unfavourable prognosis, but did not reach a statistical significance due to the small number of cases.

Other mutations in T-LBL

Mutations in NRAS and KRAS are not as frequently described in T-LBL in comparison to paediatric T-ALL, often presenting as single nucleotide variants (SNVs) (Perentes et al., 2004; Balbach et al., 2015). The mutations reported activate the RAS pathway, but no association to adverse outcome could be drawn in paediatric T-ALL (Perentes et al., 2004). Mutational analysis of PIK3R1 and PIK3CA that, similar to the PTEN mutations, result in activated PI3K-AKT signalling, also could not be clearly linked to clinical outcome due to small case numbers (Balbach et al., 2015). Mutations in the RAS and the PI3K-AKT pathway are not sufficient to reach statistical prognostic relevance as single markers, but may be relevant as a component of a more advanced molecular marker risk group stratification (see below).

miRNAs and lncRNAs in T-LBL

Comprehensive information about mutations in protein coding and noncoding regions, such as the 3’UTRs, enhancer regions (Puente et al., 2015) and noncoding transcripts, such as microRNAs (miRNAs) that have implications in haematological malignancies, is available and the potential of miRNA profiling in diagnosis and classification of cancers has been shown (Lu et al., 2005), but miRNA-profiling data with respect to T-LBL is scarce. Recently published data identified 48 miRNAs that are upregulated and 2 miRNAs that are downregulated in T-LBL (Mussolin et al., 2014). Some, like MIR221, have been shown to have a role in leukaemia (Gimenes-Teixeira et al., 2013). Pathway analysis of the
affected miRNAs show target genes that impact NOTCH1 and TCR signalling pathways. No studies have been published investigating the role of long noncoding (lncRNAs) in T-LBL. However, miRNAs and/or lncRNAs may provide future valuable tools as prognostic markers in stratification of T-LBL.

**Proposed T-LBL genetic classifier**

Based on the known genetic markers for paediatric T-LBL, Balbach et al (2015) proposed a first draft of a prognostic genetic classifier for risk group stratification:

- **Good-risk (GR) group** - NOTCH1 mutation but no RAS or PLK3-AKT pathway mutations,
- **Intermediate-risk (IR) -** all non-GR and non-high risk patients, and
- **High-risk (HR) which is defined by NOTCH1 wild type** in combination with PTENmut and LOH6q positive patients.

This classification was applied to a previously described cohort of 114 uniformly treated paediatric T-LBL. The HR group could be subjected to treatment intensification (including options of intensified chemotherapy similar to treatment of high risk ALL-patients, new drugs and allelic stem cell transplantation in first remission). The GR group could be entitled to treatment de-escalation (Fig 1). Therefore, possible approaches could include modifications of steroid administration, e.g. alternating steroid protocols. Careful validation of the prognostic impact of molecular aberrations is proposed to avoid serious consequences of increased toxicity and avoidable relapses. This proposed classifier system differs from the adult T-ALL classifier (Trinquand et al, 2013) in respect to the impact of FBXW7, LOH6q, and PIK3R1 and PIK3CA status, but shares the impact of NOTCH1 and PTEN mutations. Furthermore, the adult T-ALL classifier, when applied on the same cohort of paediatric T-LBL patients mentioned above (n = 114) defined two groups of T-LBL but failed to discriminate risk groups. Currently the proposed genetic classifier is under validation using an international collaborative approach.

**Future directions of molecular T-LBL profiling**

The epigenetic signature of T-LBL is currently unknown, but may add relevant pathogenetic insights. Mutations in genes regulating epigenetic pathways are one of the key regulators of malignant transformation of haematopoietic progenitor cells by modifications of DNA and histones that regulate gene expression. DNA methylation, particularly hypermethylation of the promoter regions, is a recurrent mechanism of gene silencing in several cancers (Roman-Gomez et al, 2007) and is associated with aggressive phenotypes and poor prognosis.

With the emergence of new and rapidly evolving next generation sequencing technology, genome-wide profiling studies has enabled the study of not only gene mutations using whole genome sequencing (WGS) and whole exome sequencing (WES), but also has allowed the study of genome organization using chromatin conformation capture techniques (Genome conformation capture-related [HiC], Circularized Chromosome Conformation Capture [4C], Carbon-Copy Chromosome Conformation Capture [5C]). Chromosomal conformation techniques enable screening for rare chromosomal rearrangements and translocation events in small subpopulations of cells. However, these technologies have not yet been exploited fully in the field of T-LBL research.

**Treatment**

With ALL-type treatment regimens, outcome of paediatric T-LBL patients has improved, with EFS rates of 75–90%, as summarized in Table I. Most current protocols are derived from either the LSA2L2 regimen that was established in the US (Memorial Sloan-Kettering Cancer Center) or the NHL-BFM protocol based on the ALL-BFM strategy (Wollner et al, 1976, 1979; Reiter et al, 1995, 2000). During the last few decades, almost all subsequently developed treatment regimens are based on one of these pioneer protocols that represent major achievements in the therapy of paediatric T-LBL.

There is limited data regarding Asian paediatric T-LBL patients with few studies published (Sun et al, 2008; Jin et al, 2012; Kobayashi et al, 2014). Results of a retrospective Chinese cohort study on paediatric T-LBL patients treated with one of three treatment protocols (CCCG-99, SCMC-T-NHL-2002 or LBL-CHOF-2006) revealed outcomes in the range of 64% for all patients. However, patient numbers were small (Gao et al, 2014) (Table I). Recently, data on 136 analysed Japanese paediatric LBL patients with advanced disease were published (Sunami et al, 2015) (Table I), which confirmed, by univariate analysis, the results of a previous Japanese report that showed an inferior outcome of T-LBL patients presenting with stage III compared to stage IV (Kobayashi et al, 2014).

In contrast to T-ALL treatment regimens, the only parameter for risk group stratification for patients with T-LBL is disease stage at diagnosis, which groups into treatment for limited (stage I and II) and advanced stages of disease (stage III and IV). However, this stratification system is unsatisfactory, as the vast majority of T-LBL patients are diagnosed with stage III/IV disease.

**Treatment of limited disease T-LBL**

Favourable pEFS for paediatric LBL patients with limited disease were achieved in the COG A5971 trial (Termuhlen et al, 2012). Notably, only eight of the 56 eligible patients presented with a T-cell immunophenotype, highlighting that
most T-LBL patients present with advanced stage (III or IV) at time of diagnosis (Burkhardt et al, 2005). Recent clinical trials (Table I) confirm the rarity and the favourable outcome of T-LBL patients with limited stage disease: in trials LMT81, NHL BFM 90, LNH92 and SPOP96 there was no relapse reported for stages I and II (Patte et al, 1992; Reiter et al, 2000; Pillon et al, 2009; Bergeron et al, 2015). Published EFS for patients with limited stage disease who were treated according to the above named trials range from 73 ± 8% (LMT81) to 100% (LNH92). These results may be achievable with relevant dose reductions, as indicated by the NHL-BFM 90 trial, which administered no re-induction for patients with limited disease (Reiter et al, 2000). In trial LNH97, 2/4 patients with stage II disease who did not receive re-induction according to the protocol relapsed, but were reported alive after relapse (Pillon et al, 2015). Treatment durations for patients with limited disease ranged from 12 to 24 months. Whether reduced treatment is sufficient for paediatric T-LBL with limited stage (I or II) disease is still under evaluation. However, current high resolution imaging techniques might further reduce the small percentage of paediatric T-LBL patients presenting without mediastinal involvement.

Impact of high-dose methotrexate in T-LBL

To improve CNS directed treatment, several protocol modifications of methotrexate (MTX) administration were evaluated (Table I). The French LMT81 trial modified the LSA212 protocol by addition of 10 courses of high dose MTX (HD-MTX) with a resultant EFS of 75% (Patte et al, 1992). The United States POG 9404 trial analysed the effectiveness of a Dana-Farber backbone therapy with or without addition of HD-MTX in T-ALL and T-LBL patients. In T-LBL patients, in contrast to T-ALL patients, there were no significant differences in EFS in the two arms (Asselin et al, 2011). In addition, the COG trial A5971 tested a COG BFM-type regimen with different schedules of CNS-directed treatment where HD-MTX without additional intrathecal MTX in maintenance was randomized against an intensified intrathecal MTX (IT-MTX) treatment arm without HD-MTX for CNS prophylaxis. Each treatment arm was randomized with or without early intensification. There were no significant differences in EFS, and the authors concluded that either IT-MTX or HD-MTX effectively prevented CNS relapse (Termuhlen et al, 2013). A recent presentation reported the Capizzi methotrexate combined with BFM protocols in 58 LBL patients (Sterba et al, 2015). CNS-directed treatment was mainly based on frequent intrathecal injections. The EFS was reported to be of 90-8% (Sterba et al, 2015).

Treatment of CNS positive patients

Current treatment strategies for patients with CNS-positive disease are detailed in Table I. Besides systemic administration of drugs that are able to penetrate the blood-brain-barrier, an increased number of IT-MTX administrations with or without IT-cytarabine or hydrocortisone or prednisolone (triple therapy) and age-adjusted cranial irradiation up to 24 Grays, are current approaches.

Cranial irradiation was omitted for patients with CNS disease in the recent EORTC 58881 trial. In this trial, 3/119 patients were CNS positive and none suffered disease relapse in the CNS (Uytttebroeck et al, 2008). Sandlund et al (2009) published the results of St Jude trial NHL-13, again omitting cranial irradiation for CNS positive patients. In this trial, 4/41 patients presented with CNS involvement at initial diagnosis. Among the four CNS positive patients, one suffered combined bone marrow and CNS relapse (Sandlund et al, 2009). The limited number of CNS positive patients who did not receive local treatment with cranial irradiation does not allow any conclusion on the role of this treatment today.

New drugs

Survival rates in relapsed paediatric T-LBL patients are poor and, due to toxicity, there are few possibilities for salvage therapies. New targeted, less toxic drugs would be an opportunity for additional treatment in these patients. Nelerabine, a nucleoside analogue, was approved by the US Food and Drug Administration after publication of two phase-II trials in paediatric and adult patients with relapsed or refractory T-ALL or T-LBL (Cohen et al, 2008). Complete remission was achieved in 5/39 paediatric patients. Neurological toxicity has been observed and was dose-limiting (Cohen et al, 2008). The COG AALL00P2 trial assessed the safety of nelarabine administration within a NHL-BFM 86 chemotherapy backbone in paediatric T-ALL patients (Dunsmore et al, 2012). The subsequent COG phase III study, AALL0434, is designed to show the safe addition of nelarabine to a COG augmented BFM-type regimen (Winter et al, 2015). Further trials to evaluate the benefit of nelarabine in paediatric patients with T-LBL, and, even more importantly, identification and implementation of additional new drugs for high risk, refractory or relapsed paediatric T-LBL are needed.

Treatment toxicities

The most frequently observed acute and long-term toxicities in the first-line treatment of paediatric T-LBL patients include infectious complications, treatment-related mortality, osteonecrosis, pancreatitis, thromboembolic events and secondary malignancies. Table I summarizes the toxic events and secondary malignancies reported in recent trials and confirms the observations of the NHL-BFM group on 2451 patients (Wachowski et al, 2005). The rate of secondary malignancies 15 years after diagnosis was significantly higher in T-LBL patients who received LBL-type therapy according to NHL-BFM protocols (6-3% compared to patients receiving B-NHL-type therapy with 3-4%), an issue that needs to
be addressed by future trial designs (Volerman, 2015; Lee et al, 2016). Another acute and long-term toxicity associated with L-asparaginase is pancreatitis, which is one of the major reasons for discontinuation of treatment and seems to be associated with an inferior outcome (Alvarez & Zimmerman, 2000; Knoderer et al, 2007, 2008; Kearney et al, 2009; Silverman et al, 2010; Vroooman et al, 2011; Raja et al, 2014). Thrombotic events are well described in the therapy for ALL and LBL in children and adolescents. Reported risk factors comprise older age (>9 years), male gender and T-immunophenotype as well as association with L-asparaginase and steroids (Silverman et al, 2001; Athale & Chan, 2003; Giordano et al, 2003; Caruso et al, 2006; Möricke et al, 2009; Santoro et al, 2013; Hijiya & van der Sluis, 2015).

Another challenging long-term toxicity in the treatment of paediatric T-LBL is osteonecrosis. Besides the role of steroids in the development of osteonecrosis, other risk factors reported include adolescent age, female gender and different gene polymorphisms (Mattano et al, 2000, 2012; Arico et al, 2003; Burger et al, 2005; Kawedia et al, 2011; te Winkel et al, 2011; Gong et al, 2013). Thromboembolic events may be another risk factor for osteonecrosis (Badihwala et al, 2015). The NHL-BFM group analysed 345 paediatric patients with LBL and reported an osteonecrosis rate of 8.4% (29/345) with a slightly higher frequency in females and adolescents (Landmann et al, 2009).

**Conclusion and perspectives in the treatment of paediatric patients with T-LBL**

Although the past 15 years have shown marked improvement in the cure rates for T-LBL, challenges remain, including further improvement in EFS rates and reduction of treatment-related mortality. Survival after relapse or treatment failure is currently very poor, with an OS of 10–30%; long term survival was reported for few patients, most of whom received allogeneic transplants after salvage re-induction chemotherapy (Burkhardt et al, 2009; Mitsui et al, 2009; Gross et al, 2010; Pillon et al, 2015). Currently no useful prognostic parameters have been confirmed for appropriate treatment stratification of T-LBL. Hence, identification of molecular markers for T-LBL is crucial to understand the biology of the disease and to identify biologically driven risk groups. Therefore, development of a valid risk group stratification system for individualized treatment (de-)escalation is necessary to address both the issues of improving survival and reducing acute and long term toxicities as well as the rate of secondary malignancies (Fig 1). Ongoing clinical trials for paediatric T-LBL patients with, for example, risk-adapted therapy according to MDD and MRD (St. Jude NHL 16; NCT01451515), or treatment with new drugs, such as bortezomib (COG, AALL1231; NCT02112916) or nelarabine (M.D. Anderson Cancer Center, 2006-0328; NCT00501826) could reveal promising results in further improving survival rates. The development of international co-operative clinical trials and fostering further research aimed at understanding the biology of the disease could enable progress in much needed new treatment approaches for T-LBL in an efficient and time effective manner.

**Author contributions**

All authors have contributed equally in writing the manuscript and were involved in the approval of the final version.

**Conflict of Interest**

The authors declare no conflict of interest.

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