T-Cell Malignancies in Children and Adolescents: State of the Clinical and Biological Science

11

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Introduction

T-cell malignancies arise from cells of the innate and adaptive immune system. The current World Health Organization (WHO) [1, 2] classification recognizes over 20 distinct entities within the T/natural killer (NK) cell neoplasms. The more common subtypes that occur in children and young adolescents are the precursor T lymphoblastic leukemia/lymphoma and anaplastic large cell lymphoma (ALCL), anaplastic lymphoma kinase (ALK) positive. The rest are rarely observed in children. The majority of T-cell malignancies are aggressive neoplasms [3] and although rare relative to the adult population they present a formidable challenge from diagnostic and therapeutic perspectives. In this chapter, we provide an update of the clinical and biologic features of the common T-cell malignancies that occur in children and adolescents with a focus on molecular perspectives and implications for novel therapeutics.

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T-Cell Acute Lymphoblastic Leukemia in Children and Adolescents

Acute lymphoblastic leukemia (ALL) is the most prevalent type of cancer occurring in children and adolescents in the Western World. A lymphoid malignancy derived from early progenitor cells in the bone marrow, it represents a heterogeneous group of diseases comprising multiple subtypes with biologically different behaviors. T-cell lineage ALL is a less common subtype, accounting for approximately 15% of cases [4]. T-cell acute lymphoblastic leukemia (T-ALL) is associated with numerous unfavorable clinical factors and carries a worse prognosis than its counterpart precursor B-cell ALL (B-ALL) [4]. Children with T-ALL are more likely to manifest with National Cancer Institute (NCI) high-risk features such as WBC >50,000 at diagnosis, older age, and central nervous system (CNS) involvement. They are also more likely to have bulky disease with enlargement of the liver, spleen, lymph nodes, and to have a mediastinal mass [4].

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Table 11.1 Outcome in childhood T lymphoblastic leukemia: twenty-first century results

References	Goldberg et al. [7]	Moghrabi et al. [8]	Ballerini et al. [6]	Moricke et al. [9]	Pui et al. [10]
Institution/group	DFCI	DFCI	FRALLE	BFM	St. Judes
Protocol/treatment	87-01, 91-01, 95-01	95-01	FRALLE-93	ALL BFM-95	Total therapy XV
Number of patients	125	52	200	275	76
EFS (%)	75 ± 4	85 ± 6	58 ± 3	70 ± 3.3	80 ± 8.7

Although improvements have been achieved in outcomes with conventional chemotherapy regimens, event-free survival (EFS) rates for children with T-ALL in some series may be inferior to those for children with precursor B-cell ALL. As discussed in the following section on T-cell lymphoblastic lymphoma (T-LBL), there are important biological and clinical differences between T-LBL and T-ALL despite the overarching similarities. The same is to be said in comparing B-ALL and T-ALL. Inasmuch, with continued advances in the understanding of the unique characteristics of T-ALL, there is hope for even further improvement of outcomes with development of new treatment strategies.

Unlike T-LBL, which often presents with systemic B-symptoms and complications of supradiaphragmatic lymphadenopathy, T-ALL is more likely to present with fever, bone pain, and the typical symptoms associated with cytopenias-petechiae and/or easy bruising, fatigue and pallor, and infection [5]. However, since T-ALL is more likely than precursor B-cell ALL to present with significant lymphadenopathy, hepatosplenomegaly, and a mediastinal mass, the clinical symptoms associated with T-ALL can overlap with those of T-LBL [5]. The distinction would therein be that ALL is defined by having more than 25% involvement of the bone marrow with lymphoblasts. Flow cytometry studies are critically important in making an accurate distinction between the immunophenotypes of B and T lymphoblasts.

Treatment regimens for T-ALL have achieved significant improvements over the past 25 years through the introduction of intensive, high-dose, multi-agent chemotherapy regimens. Most contemporary protocols treat pediatric T-ALL with the same regimens given to children with high-risk B-ALL. Using multi-agent intensive regimens, several pediatric oncology cooperative groups including the Children's Oncology Group (COG [formerly Children's Cancer Group (CCG)]), Dana Farber Cancer Institute (DFCI), Berlin-Frankfurt-Munster (BFM), French ALL Cooperative Group (FRALLE), and St. Jude's ALL protocols over the past decade have consistently reported EFS rates ranging from 58 to 85% for children with T-ALL (Table 11.1 and Fig. 11.1) [6–13]. These regimens are similar in execution, utilizing treatment programs of greater than 2 years in duration, employing phases focused on remission induction, consolidation, intensification, CNS-directed therapy, and maintenance, as well as combining multiple chemotherapeutic agents. Chemotherapy frequently used across protocols includes glucocorticoids (prednisone and/or dexamethasone), anthracyclines, methotrexate (MTX) (at high and low doses), vincristine, asparaginase, 6-mercaptopurine, and cyclophosphamide. Many high-risk regimens will also incorporate cytarabine and etoposide into the combination. Intrathecal (IT) chemotherapy is given universally utilizing MTX, cytarabine, and hydrocortisone. Until recently, all treatment protocols utilized cranial radiation therapy (CRT) for patients with CNS disease, as well as those with high-risk for CNS relapse, which includes children with T-ALL.

The St. Jude's group just completed their analysis of 498 ALL patients treated without the use of CRT. It was a landmark protocol in that even those patients who were CNS positive at diagnosis did not receive radiation. Based upon the rate of CNS relapse in comparison with historical controls that received CRT, the results demonstrated that omission of CRT was safe and associated with EFS and overall survival (OS) rates

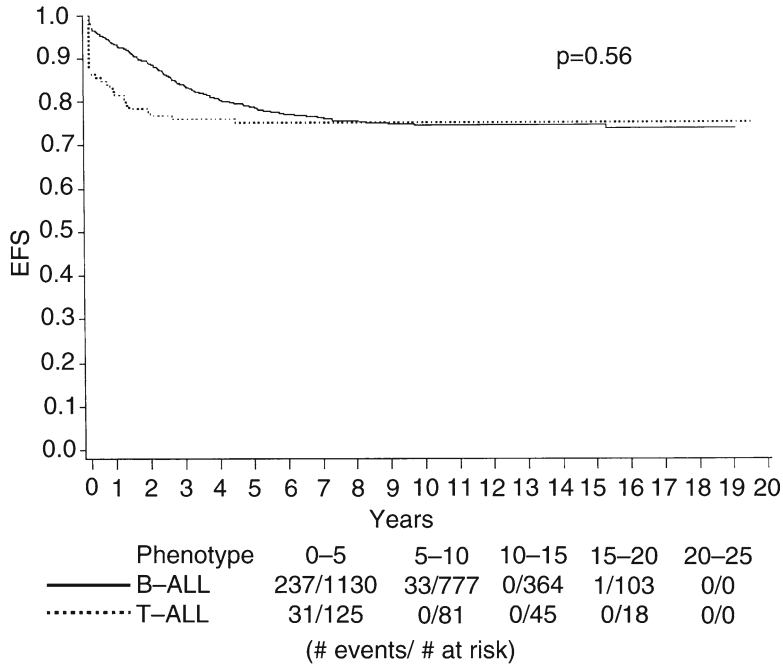

Fig. 11.1 Event-free survival (EFS) by immunophenotype. Children with B-progenitor acute lymphoblastic leukemia (B-ALL, _____) had an EFS rate of 79% ± 1%. Children with T-cell acute lymphoblastic leukemia ALL (T-ALL, - - -) had an EFS rate of 75% ± 4% ($P = 0.56$). Early events are more common in T-ALL (reprinted from Goldberg et al. [7], with permission from American Society of Clinical Oncology)

comparable to prior protocols that utilized CRT. However, patients with T-ALL (in addition to those that were CNS positive at diagnosis and children with the t1;19 translocation) had a remarkably high hazard ratio for risk of CNS relapse, despite having received higher doses of MTX than in standard regimens (it has been shown that T-lineage lymphoblasts have a decreased affinity for uptake of MTX substrates and that higher doses are required to overcome this pharmacodynamic challenge) [14]. The authors make the argument that these patients nonetheless, should be treated without CRT regardless of the CNS relapse risk. Their rationale is that otherwise nearly 90% of this risk group of patients will thereby receive CRT that could have been avoided. Certainly the counterpoint can be made that until we are able to more accurately predict which subgroup of children with T-ALL are at an especially high risk for CNS relapse, they should all uniformly receive CRT. Overall, T-ALL patients on this protocol had an EFS of 78% which is comparable with prior treatment regimens [10].

The best EFS rate to date for patients with T-ALL was reported on the DFCI 95-001 treatment regimen (Table 11.1). They also treated T-ALL patients similar to the therapy for the high-risk B-ALL subgroup. However, their high-risk treatment regimen was notable for an increased overall dose of asparaginase and additional doxorubicin. This treatment regimen did include CRT for T-ALL patients. The 5-year EFS was 85%, which is remarkably favorable compared to all other large series of patients with T-ALL. In fact, children with T-ALL fared better on this protocol than those with pre-B ALL. The authors attributed the favorable outcome to the efficacy of the high-risk treatment regimen, but it is perplexing that the high-risk pre-B ALL patients did not fare better as well [8].

Relapsed ALL of both B and T-cell lineages presents an enormous challenge to the goal of achieving long-term cure. Only about one-third

of patients with relapsed ALL will experience long-term survival despite intensive re-induction regimens including the utilization of allogeneic stem cell transplantation (alloSCT) [15]. Patients with early relapse are defined as occurring less than 36 months after initial diagnosis; early relapse portends a particularly dismal prognosis with less than 20% 3-year EFS [16]. It is difficult to comment on the prognosis of relapsed T-ALL as results are only occasionally reported as subsets within already small numbers of patients of relapsed ALL in general. In a recent COG analysis of children with ALL in first relapse, 7/124 patients had T-ALL, only 2 out of those 7 achieved a second remission, and no T-ALL patient lived longer than 10 months [17]. Another COG analysis of children with early relapse of ALL had 28 patients with T-ALL and an EFS of <5% for that subgroup of patients [16]. New developments in treatment strategies for relapsed T-ALL are desperately needed.

Nelarabine is a novel agent that has shown promise in relapsed and refractory T-ALL but not T-LL. It is a purine analog whose mechanism of action delivers markedly specific toxicity to T lymphocytes. The use of Nelarabine in T-cell malignancies was first investigated based upon the observation that patients with purine nucleoside phosphorylase (PNP) deficiency suffer from T-cell immune deficiency due to the abnormal and toxic accumulation of deoxyguanosine triphosphate (dGTP) in T cells. Nelarabine is a derivative of dGTP and is resistant to degradation by PNP. In a phase II COG study, patients with T-ALL in first relapse (not involving the CNS) had a response rate of 55% (with 16 of 33 patients achieving a complete remission [CR]). CNS toxicity ≥grade 3 was experienced in 18% of patients, manifesting as peripheral neuropathy, seizure, and hallucinations. The promise of such extraordinary results in a historically extremely high-risk group of patients has led to the investigation of Nelarabine's utility in front-line therapy for children with high-risk T-ALL [18].

Two groups of T-ALL patients that demonstrated an especially high-risk for treatment failure are those who are poor initial responders to prednisone and those with minimal residual disease (MRD) at the end of induction therapy. The BFM cooperative group demonstrated that children with T-ALL that exhibit a poor response to 1 week of prednisone plus IT MTX on day 1 have an EFS of 32% compared to 78% in good responders. Poor response was demonstrated as having ≥1,000 leukemic blasts/μL peripheral blood on day 8 of induction [19]. The presence of MRD at the end of induction in patients with ALL has been an ominous prognostic sign for both pre-B and T-ALL, with as high as a 70% chance for early relapse. Patients with T-ALL have demonstrated an even higher risk of being MRD positive than their B-ALL counterparts [20–22]. These risk factors have thereby served as a platform for building clinical trials investigating the role of new drugs in improving overall EFS for patients with T-ALL.

The current COG study (AALL-0434) is one of the few ALL protocols designed specifically for patients with T-ALL. Utilizing a BFM ALL treatment backbone, it is investigating the use of Nelarabine and high-dose MTX in the treatment of intermediate and high-risk T-ALL. Risk stratification is based upon the aforementioned prognostic factors. High-risk patients are those with positive MRD (or gross induction failure) at end of induction. Low-risk patients are CNS negative, low-risk by NCI standards for age and initial WBC, exhibit good response to initial 1 week of prednisone, and are MRD negative. Intermediate-risk patients do not fit the low-risk category, but are MRD negative at the end of induction. In preliminary pilot data from COG study AALL-02P2, higher-risk patients receiving Nelarabine fared as well as their low-risk counterparts not receiving the drug. More specifically, patients with a poor response to prednisone that received Nelarabine in combination therapy achieved an equivalent 3-year EFS of 75% in comparison to those with a good response that did not receive Nelarabine. Moreover, this was achieved without the Nelarabine group experiencing excess toxicity [23]. Improvement of the cure rates for patients with high-risk T-ALL offers significant opportunity to improve on the EFS for patients with T-cell lineage ALL overall.

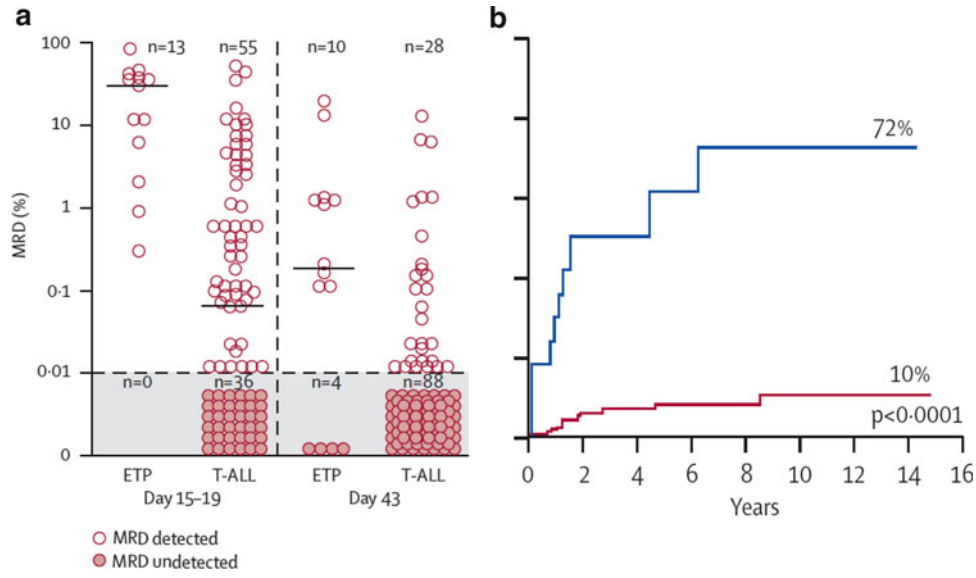

Fig. 11.2 (**a**) Prevalence of minimal residual disease (MRD) during the early phases of therapy for patients with early T-precursor (ETP) or typical T-ALL. MRD levels were measured by flow cytometry (**a**). *Horizontal bars* indicate median values, if above 0.01%. (**b**) Kaplan–Meier plots of the cumulative incidence of remission failure or hematological relapse in patients with typical T lymphoblastic leukemia (T-ALL; *red*) vs. early T-cell precursor (ETP)-ALL (*blue*) treated on St. Jude protocols. The curves start at the time of diagnosis. Outcome estimates at 10 years of follow-up are shown; *P* values are from the log-rank test (reprinted from Coustan-Smith et al. [24], with permission from Elsevier)

Recently, another smaller subset of patients with T-ALL has also demonstrated a markedly poor prognosis [24]. Lymphoblasts characterized by an immunophenotype of early T-cell precursors (ETP-ALL) seem to have a distinct biology in comparison to typical precursor T lymphoblasts. The early precursors tend to retain stem-cell-like features and exhibit genomic instability. Of 239 patients investigated with T-ALL, 30 were found to have the ETP-ALL subtype. Of patients with ETP-ALL, there was a significant increase in MRD at day 18 and day 43, resulting in a significant increase in the risk of remission failure and/or hematologic relapses [24]. There was a 72% risk for failure or relapse at 10 years in patients with ETP-ALL vs. 10% for patients with typical T-ALL treated at St. Jude's Children's Research Hospital (Fig. 11.2a, b). Currently the St. Jude's treatment protocols have been adjusted to modify therapy by introducing alloSCT in CR1 for patients with ETP-ALL [24].

The BFM and CCG cooperative groups have previously examined the role of alloSCT in CR1 for patients with high-risk disease [25, 26]. The BFM group defined high risk as those having a poor response to prednisone and/or the inability to achieve remission with induction chemotherapy [26]. The BFM group compared outcomes of 179 patients that achieved CR1, 23 of whom received an alloSCT (8 from matched unrelated donors, 15 from sibling donors). The 5-year OS for patients who received an alloSCT was 67% vs. 47% for those who received only chemotherapy (Fig. 11.3) [26]. While the utility of alloSCT represents a reasonable treatment escalation strategy for the high-risk group of T-ALL patients, it remains to be seen whether the encouraging results from the Nelarabine trials in front-line therapy may offset the survival advantage seen in patients treated with alloSCT in CR1.

Another developmental therapeutic strategy is based upon the unraveling of the Notch pathway involvement in the pathogenesis of T-ALL. The Notch family of transmembrane receptors is critically involved in cell differentiation, proliferation, and apoptosis pathways (see section on

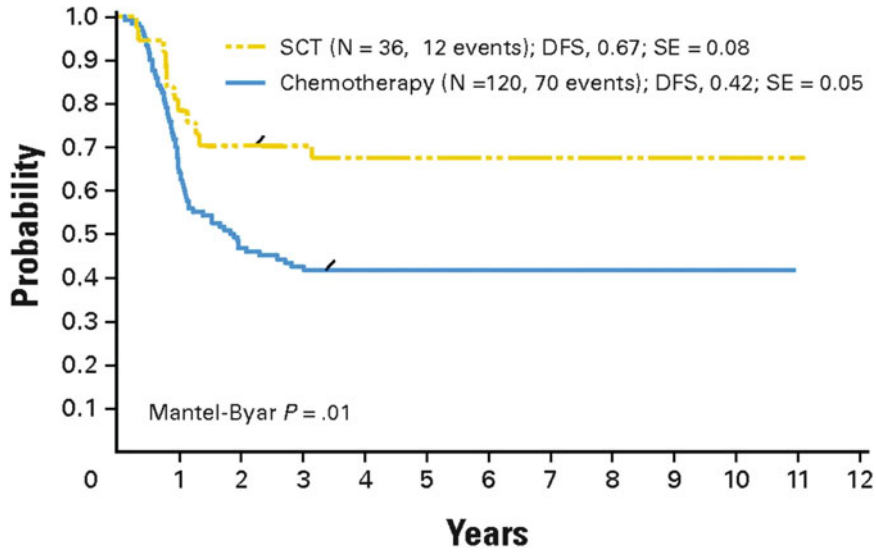

Fig. 11.3 Kaplan–Meier estimate of disease-free survival (DFS) at 5 years in stem-cell transplantation (SCT) patients vs. patients treated with chemotherapy alone (Acute Lymphoblastic Leukemia-Berlin-Frankfurt-Munster trials 90 and 95; analysis as treated). From the group of patients treated with chemotherapy alone, patients with an event before 0.43 years (medium time to transplantation) were excluded (reprinted from Schrauder et al. [26], with permission from American Society of Clinical Oncology)

molecular basis of pediatric T-ALL) [27]. Activating Notch mutations have been found in 50–60% of human T-ALL samples [28]. Gamma-secretase inhibitors (GSIs) are a family of drugs that inhibit the activation of Notch1 and their utility in the treatment of T-ALL has been under investigation. GSIs in combination with glucocorticoids can exhibit potent anti-leukemic effects *in vivo*, while combination of the two medicines results in a decrease of the dose-limiting gastrointestinal toxicities seen with GSIs. The effect of this combination also revealed the ability to induce apoptotic cell death in leukemic cells that were prior considered glucocorticoid-resistant [29]. It has also been shown that Notch positively regulates the mTOR pathway with c-Myc as a potential intermediary. Combination treatment with GSIs plus an mTOR inhibitor has shown synergistic effects against T-ALL cells in both *in vitro* and *in vivo* models [30, 31]. In addition, GSIs have also been combined in preclinical models with the proteasome inhibitor bortezomib and P13K-AKT inhibitors [32, 33]. Ultimately, after it seemed curative effects in T-ALL had plateaued after many years of unwavering EFS rates, promising new therapies targeting specific characteristics of T-cell pathology are offering exciting new hope for physicians, scientists, and patients alike.

T-Cell Lymphoblastic Lymphoma in Children and Adolescents

Lymphoblastic lymphoma (LBL) is the second most common type of childhood non-Hodgkin lymphoma (NHL) after Burkitt lymphoma (BL). The vast majority (80–90%) of cases of LBL are derived from the T-cell lineage, in contrast to ALL, in which most cases are precursor B-cell in origin. This renders T-LBL the most common type of T-cell lymphoma occurring in children [34–36]. For many years T-LBL and T-ALL were thought to be diseases on different ends of a single spectrum of pathology, but recent advances in the understanding of the biology of lymphoblastic disease have shed light on some important differences amidst the many shared commonalities [37, 38]. Furthermore, there are some important clinical distinctions between T-LBL and T-ALL.

Table 11.2 Advanced disease lymphoblastic lymphoma in children

	BFM [218]	St. Jude [219]	EORTC-CLCG [220]	DFCI [221]	UKCCSG [222]	CCG [223]
Patients (*N*)	101	24	60	21	95	102
Protocol	NHL-BFM-90	Total therapy-X	EORTC 58881	APO	UKCCSG 8503	CCG 5941
Duration (months)	24	32	24	24	24	12
EFS (Est) 3–6 years	90%	73%	76%	58%	65%	79%

Reprinted from Cairo [34], www.jbpub.com, with permission from Jones and Bartlett
EFS event-free survival; *Est* estimate

While T-LBL tends to have localized and earlier relapse than its counterpart, T-ALL tends to have more frequent CNS involvement at initial diagnosis [39–41].

Childhood T-LBL commonly presents with a supradiaphragmatic mass and as advanced stage III/IV disease, while B-cell LBL tends to present with limited disease in sites including the skin, bone, and peripheral lymph nodes. Typically, T-LBL may present as an adolescent male with respiratory distress found to have an anterior mediastinal mass. Severe complications can potentially arise from a supradiaphragmatic mass including respiratory failure and superior vena cava (SVC) syndrome warranting emergent intervention with steroids and/or radiation therapy. Disease may also involve the bone marrow and CNS; however, one must keep in mind that greater than 25% involvement of the bone marrow with lymphoblasts is referred to as lymphoblastic leukemia, while >5% but <25% involvement of the bone marrow would be termed stage IV LBL [42].

Children with limited disease T-LBL have a favorable prognosis with long-term OS of 85–90% [34–36, 42]. Although disease free survival (DFS) rates are only 63–73%, children with limited disease (Murphy stages I and II) have favorable responses to salvage therapies. ALL-based treatment protocols have been the mainstay of therapy for this group of children with T-LBL [43, 44]. Patients with localized disease are currently being treated without local surgical intervention, local radiation therapy, and CRT. However, most cases of T-LBL are advanced stage, so the focus of the treatment discussion will be on therapeutic approaches for children with advanced stage III/IV disease.

The prognosis for children with advanced stage T-LBL improved significantly after the introduction of the 10-drug LSA_2L_2 regimen in the 1970s [45]. From that point forward, most treatment protocols for LBL have been based upon the combination of corticosteroids, vincristine, anthracyclines, L-asparaginase, cyclophosphamide, MTX, cytarabine, 6-mercaptopurine, and 6-thioguanine. The BFM regimens employ an ALL backbone therapy with some adjustments, while many other regimens have been based on the LSA_2L_2 regimen with various modifications. Nearly all contemporary strategies are divided into stages that include induction, consolidation, re-intensification, and maintenance chemotherapy. The timing and dosing of some specific medicines may vary, but overall most protocols reported since the year 2000 have been able to achieve a 75–90% EFS with regimens ranging from 12 to 24 months duration (Table 11.2).

The highest EFS reported to date was from the BFM-90 protocol in which patients with advanced stage disease all received CRT, regardless of whether or not they had CNS involvement. The EFS was 90% for stage III/IV patients; however due to the deleterious long-term effects of CRT, subsequent studies have focused on the safety and efficacy of omitting CRT (Fig. 11.4a) [40]. Multiple studies have investigated protocols in which CRT was only utilized in patients with CNS positive disease. The Italian AIEOP LNH-92 protocol reported an EFS of 65% in advanced stage T-LBL; however they notably did not implement a re-intensification phase after induction and consolidation therapy [46]. The BFM-95 protocol also administered CRT to patients with

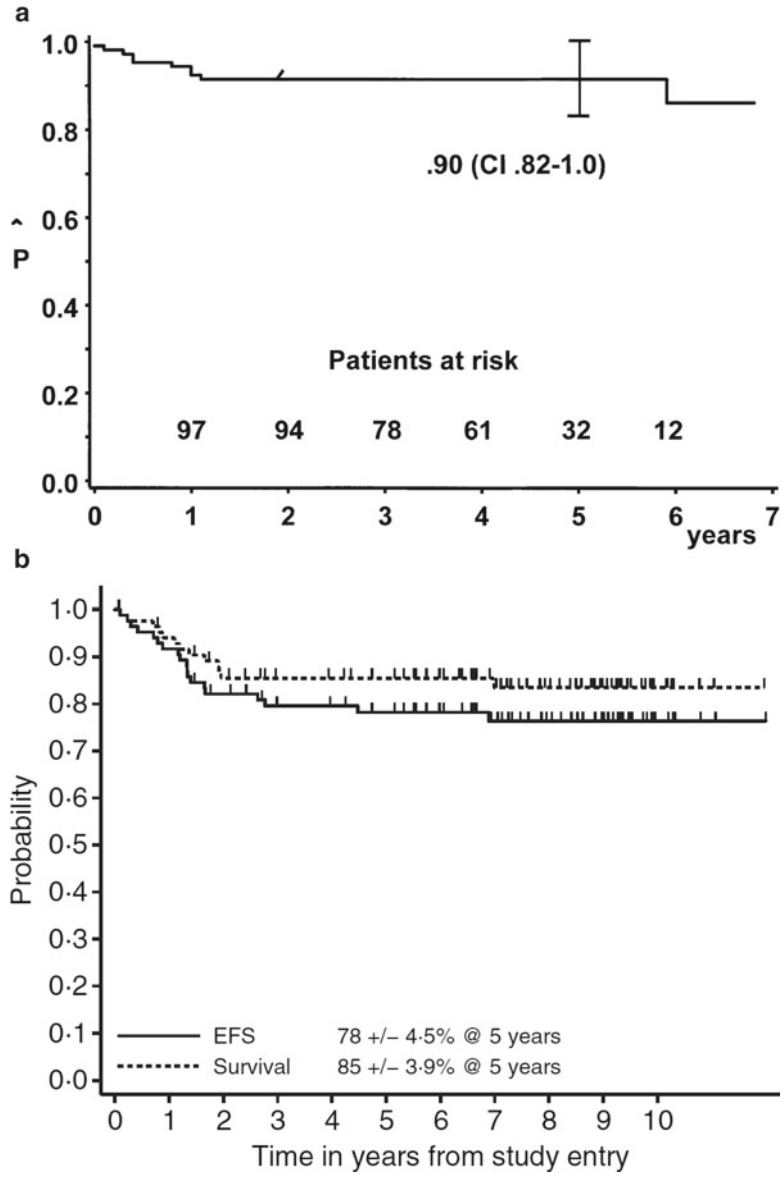

Fig. 11.4 (**a**) Probability of duration of EFS and 95% confidence bands. This research was originally published in *Blood* [40]. © American Society of Hematology. (**b**) Probability of EFS and overall survival (survival) of all patients from diagnosis (reprinted from Abromowitch et al. [48], with permission from Wiley-Blackwell Publishing)

CNS positive disease only, choosing to optimize delivery of high-dose MTX and IT chemotherapy. In a historical comparison to their earlier protocols including BFM-90 and 86, they determined that omitting CRT may be non-inferior to treatment including CRT in CNS negative patients. However, the EFS for advanced stage LBL in the BFM-95 protocol was 82%, lower than that of the BFM-90 study [47]. The COG reported on a shortened (12-month) intensified multi-agent chemotherapy regimen for advanced stage disease, also only administering CRT to patients that were CNS positive. This strategy yielded a 5-year EFS of 78% concluding that the shortened approach was safe and achieved similar results as more prolonged ALL-based regimens

(Fig. 11.4b) [48]. The most recent COG study for T-LBL examined whether the effects of high-dose MTX and early intensification of therapy with anthracycline and cyclophosphamide would further improve DFS. Preliminary data shows that neither high-dose MTX nor early intensification in BFM-type ALL therapy resulted in improvement in EFS for T-LBL [49].

Recently, the European Organisation for Research and Treatment of Cancer (EORTC) and St. Jude's have employed treatment protocols entirely omitting CRT, even in patients who are CNS positive. The EORTC CLG 58881 trial utilized a BFM-based regimen and achieved a 6-year EFS of 78% for advanced stage disease. They successfully demonstrated that omission of CRT did not influence the rate of CNS relapse. And notably, they also established treatment response to the 7-day prednisone-only prephase as a significant prognostic factor. Patients with a CR after the prephase (16 out of 121) had an EFS of 100%, contrasting with an EFS of 14% for those with no response to the prephase [50]. The NHL13 protocol utilized by the group at St. Jude's was based on their institutional ALL therapy including a maintenance phase with alternating pairs of therapeutic agents and incorporating high-dose MTX every 8 weeks in addition to a re-induction regimen 16 weeks into the maintenance phase. They were able to demonstrate an excellent EFS rate of 83% for advanced stage T-LBL despite omission of CRT as well. The study however only analyzed 41 patients, in comparison to the other studies discussed above in which the number of patients ranged from 85 to 156 [51].

The majority of children who relapse/progress do so within 24 months of diagnosis and the prognosis for children who develop recurrent disease is poor, with less than a 10% 5-year OS (Fig. 11.5a) [39, 52]. In an effort to improve outcome for patients with relapsed disease, intensive re-induction chemotherapy followed by either autologous (auto) or alloSCT improved DFS to between 23 and 58% [53–55]. Retrieval chemotherapy has included NHL regimens such as DECAL (dexamethasone, etoposide, cisplatin, high-dose cytarabine and L-asparaginase) [56] and ICE (ifosfamide, carboplatin, and etoposide) [57]. Patients with disease that is chemosensitive to the retrieval regimen have better outcomes following either auto or alloSCT [57, 58]. In a retrospective comparison of auto vs. alloSCT, significantly lower relapse rates were observed following alloSCT vs. autoSCT; however higher treatment-related mortality offset any survival benefit [59, 60]. In a more recent analysis from the BFM, OS was 14% among 28 patients with relapsed T-LBL (Fig. 11.5b). They all went on to receive salvage therapy, while 9 patients went on to receive an alloSCT. Of those who received an alloSCT, 4 were still alive >4 years post-alloSCT. The two patients that received autoSCT succumbed to their disease [39]. Although these numbers are too low to derive any statistically significant conclusions, it remains that any chance for survival in this group of patients with relapsed or progressive T-LBL depends upon a sufficient response to salvage chemotherapy and a successful alloSCT. The development of newer therapies for T-LBL has not met much success. Nelarabine has been shown to have a significantly more substantial effect on refractory T-ALL than T-LBL [18]. In terms of targeted therapies, the upregulation of Notch and the associated mTOR protein kinase pathway has stimulated investigation to the effects of mTOR and/or Notch inhibition *in vitro* [61]. And finally, phase I studies have been undertaken examining the role of Forodesin in T-cell malignancies, although mostly in adults with peripheral T-cell lymphoma (PTCL). Forodesin is a PNP which was recognized more than 30 years ago as a potential target for the treatment of patients with T-cell malignancies when an inherited deficiency of PNP was reported to be associated with a profound T-cell lymphopenia [62].

With such dismal salvage rates in LBL, accurate delineation of prognostic factors to identify patients at high risk of relapse is vitally important. Unfortunately though, definitive prognostic factors in childhood T-LBL have yet to be well established. Aside from the striking results of the EORTC CLG trial in which treatment response to the 7-day prednisone prephase demonstrated polar extremes of eventual EFS rates, clinical

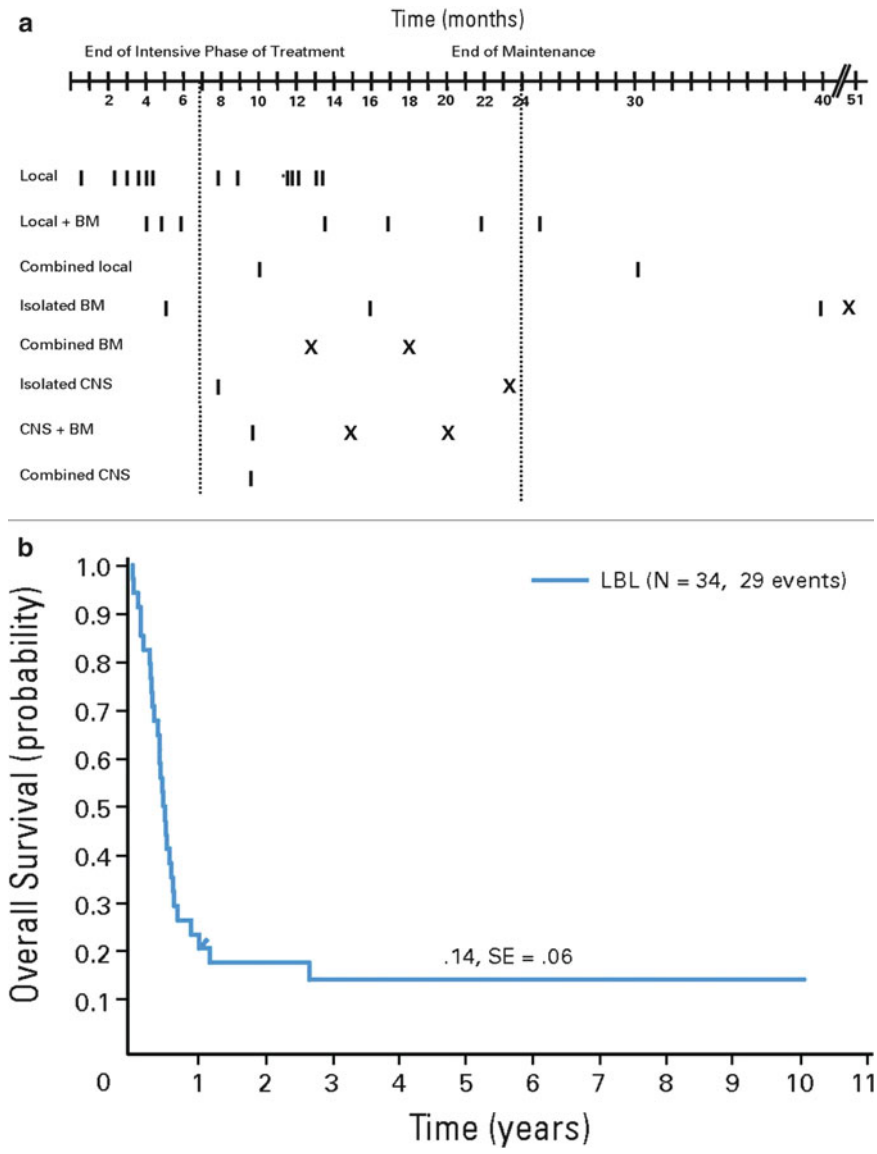

Fig. 11.5 (**a**) Time and site of disease progression or relapse in children with relapse of a lymphoblastic lymphoma (LBL). *I*, patients with T-cell lymphoblastic lymphoma; *X*, patients with precursor B-cell lymphoblastic lymphoma; *BM* bone marrow. (*)This patient was treated according to high-risk arm and experienced relapse during intensive phase of treatment 11 months after start of therapy. (**b**) Probability of survival at 5 years for children with disease progression or relapse of LBL (reprinted from Burkhardt et al. [39], with permission from American Society of Clinical Oncology)

prognostic factors have not been elucidated. The assessment of treatment response, either by laboratory or radiographic monitoring (including 2-Deoxy-2-[18F]fluoro-D-Glucose positron emission tomography [FDG PET]), is a potential method of identifying high-risk patients and determining prognostic parameters to guide therapeutic adjustments for patients that require intensification of up-front therapy [63].

T-LBL has a scarcity of cytogenetic and molecular factors associated with poor response to therapy. Recently, however, there have been

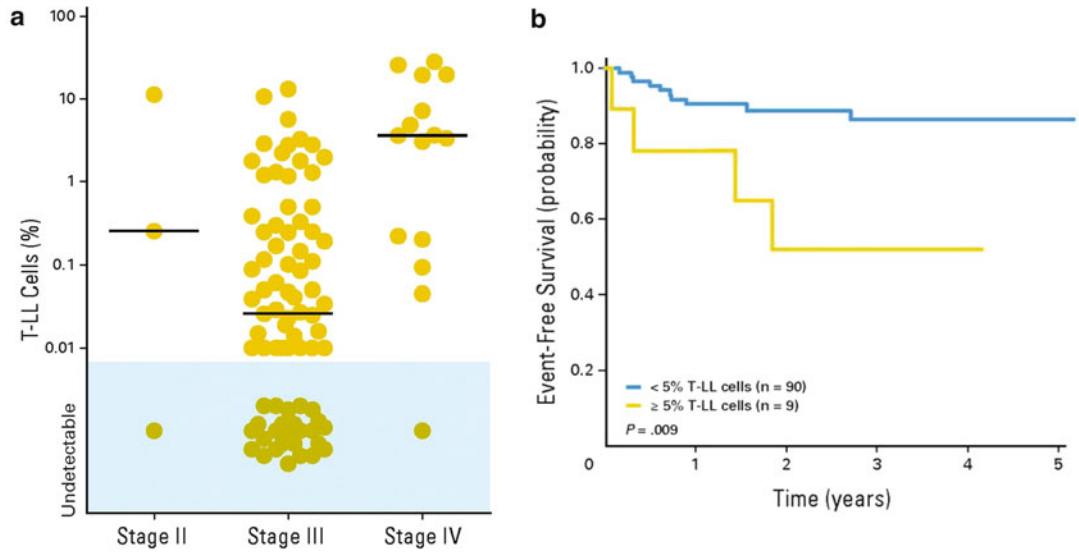

Fig. 11.6 (**a**) Percentage of T-cell lymphoblastic lymphoma (T-LL) cells in bone marrow at diagnosis as detected by flow cytometry according to disease stage based on conventional criteria. *Horizontal bars* indicate the median value in each group. (**b**) EFS according to levels of T-LL cells in bone marrow at diagnosis measured by flow cytometry: (**a**) <5% and ≥5% T-LL cells (reprinted from Coustan-Smith et al. [65], with permission from American Society of Clinical Oncology)

some interesting studies shedding light on potentially important prognostic factors. Loss of heterozygosity at chromosome 6q was associated with an increased risk of relapse in T-LBL [37]. Meanwhile, substantial advances have been established in the ability to detect levels of minimal disseminated disease (MDD) and MRD. T-cell receptor (TCR) real-time quantitative polymerase chain reaction (PCR) assays have been successfully utilized as a technique to assess and monitor MDD and MRD in T-LBL [64]. In a recent analysis of flow cytometry methods of detecting disease at molecular levels in 99 patients, two-thirds were found to have MDD in the bone marrow at diagnosis, and of those with ≥5% T-LBL cells in the marrow, the 2-year EFS was 51.9% vs. 88.7% for those patients with lower levels (Fig. 11.6a, b). The analysis reveals a very striking trend towards poor response to therapy and the presence of MDD and provides a foundation for further studies to examine the relationship between MDD and risk for relapse [65]. Having encountered a relative ceiling in the inability to significantly improve EFS in the treatment of advanced stage LL over the past decade, development of accurate prognostic factors will likely serve as the key to future improvements in outcome. Ultimately, it will be crucial to determine subgroups of high-risk patients that will benefit from alternative and intensified modalities of treatment including alloSCT as first line strategies.

Molecular Basis of T-ALL/T-LBL in Children and Adolescents

T-ALL and T-LBL represent 15% of childhood ALL and one-third of childhood and adolescent NHLs, respectively. T-ALL is characterized by prominent (>30%) bone marrow infiltration by T-cell lymphoblasts, whereas T-LBL demonstrate mediastinal masses in the context of limited or no bone marrow involvement [66]. Both clinical entities share a similar spectrum of molecular and cytogenetic abnormalities and most probably represent different clinical manifestations of the same thymocytic neoplasm, commonly referred to as T-ALL [66]. Current treatment, mainly consisting of multi-agent combination chemotherapy, provides

an OS rate of approximately 70–90% in children and adolescents [67, 68]. Despite recent progress in the treatment of these diseases, the prognosis of T-ALL/T-LBL patients with primary resistant or relapsed leukemia is very poor, underscoring the need to develop more effective antileukemic drugs [67, 68].

Over the last 20 years, great progress has been made in unraveling molecular-genetic defects that are involved in the pathogenesis of T-ALL [69, 70]. It is now generally accepted that the leukemic transformation of immature thymocytes is caused by a multistep pathogenesis involving numerous genetic abnormalities that permit uncontrolled cell growth [66, 71].

In T-ALL, transcription factors are frequently activated due to disturbances in the rearrangement process of the TCR genes, juxtaposing the proto-oncogenes to the enhancers of *TCRβ* (7q34) or *TCRαδ* (14q11) [72]. These TCR-mediated translocations occur in approximately 33% of T-ALL cases [73] and cause deregulation of (1) basic helix-loop-helix (bHLH) family members such as *TAL1* [74–76], *TAL2* [77], *LYL1* [78], and *BHLHB1* [79]; (2) LIM-only domain (LMO) factors such as *LMO1* and *LMO2* [80–82]; and (3) the *TLX1/HOX11* [83–86], *TLX3/HOX11L2* [87, 88], *NKX2.5* [89], and *HOXA9* [90, 91] homeobox genes; *MYC* [92, 93], *MYB* [94, 95], and *TAN1*, a truncated and constitutively activated form of the NOTCH1 receptor [96]. In addition, a number of non-TCR-mediated translocations generate specific fusion products including *MLL-ENL* [97], *CALM-AF10* [98], and *SET-NUP214* [99].

From gene expression profiling studies and the analysis of T-ALL mouse models, the concept emerged that aberrant expression of these oncogenic transcription factors cause disruption of the normal circuitry that controls cell proliferation, differentiation, and survival during T-cell development [88, 90, 100]. Since these microarray studies also suggested that the transcription factor deregulations are associated with specific patterns of gene expression and a differentiation arrest at specific stages of T-cell development, these genetic lesions are thought to define different molecular-genetic subgroups in T-ALL. For example, T-ALL patients that show rearrangements of the *TAL1*, *TAL2*, *LMO1*, or *LMO2* genes are characterized by a highly similar gene expression signature, probably due to the fact that these transcription factors normally participate in the same transcriptional complex [101]. Also, *CALM-AF10*, *MLL*-rearrangements, inversion 7 positive patients, and *SET-NUP214* positive T-ALL patients share a common expression profile that is characterized by the activation of the cluster of *HOXA* transcription factors [90, 99]. Activation of other transcription factors including *TLX1*, *TLX3*, and *MYB* has each been shown to have their unique gene expression profile [88, 94, 100].

The complexity of genetic alterations associated with T-cell transformation is completed with a few highly prevalent cytogenetic and molecular alterations that occur throughout all molecular subtypes of T-ALL. The most prominent T-cell-specific abnormality is the presence of activating mutations in *NOTCH1*, which are detected in over 55% of T-ALL cases [28]. However, the most prevalent genetic lesion in T-ALL is the homozygous or heterozygous inactivation of the genomic *CDKN2A* and *CDKN2B* loci, located in tandem at chromosome 9p21, occurring in more than 70% of T-ALL cases [102]. T-ALL is further characterized by a wide variety of rare but recurrent genetic lesions which result in (1) activation of genes involved in cell proliferation such as *LCK* [103], *CCND2* [104], *JAK1* [105], *ETV6-JAK2* [106], *ETV6-ABL1* [107], *NUP214-ABL1* [108], *EML1-ABL1* [109], *FLT3* [110, 111], and *RAS* [112] and (2) inactivation of tumor suppressor genes responsible for control of cell growth including *NF1* [113], *SHIP1* [114], and *PTEN* [115]. Some other genetic defects are more restricted to specific molecular-genetic subtypes, including *WT1* mutations that are most prominently found in T-ALL cases with aberrant rearrangements of the oncogenic *TLX1*, *TLX3*, and *HOXA* transcription factor oncogenes [116].

Activation of NOTCH1 Signaling

NOTCH1 is a transmembrane receptor that plays a major role in normal hematopoiesis driving lineage commitment of lymphoid progenitor cells towards T-cell development [117]. Thus, inactivation of NOTCH1 signaling in lymphoid

progenitors in mice blocks T-cell development and promotes differentiation towards the B-cell lineage [118–120]. In the reciprocal setting, constitutive activation of NOTCH1 inhibits B-cell development and promotes extrathymic T-cell development [121].

NOTCH1 is synthesized as a single precursor protein (pre-NOTCH), which is processed by a furin protease to generate a heterodimeric protein consisting of an extracellular subunit and a transmembrane/intracellular subunit. Upon binding to the Jagged and Delta-like family of receptors, NOTCH1 undergoes two additional proteolytic cleavages which ultimately release the intracellular domains of the receptor (ICN1) in the cytosol [119, 120]. ICN1 is then transported to the nucleus where it mediates the expression of target genes such as *HES1*, *HEY1*, *MYC*, *PTCRA*, and *DTX1* [122–124].

A specific role for *NOTCH1* in human T-ALL was originally postulated due to its involvement in the rare chromosomal translocation, t(7;9)(q34;q34.3), which couples the intracellular part of *NOTCH1* to the *TCRβ* locus and leads to the aberrant expression of an intracellular constitutively active form of NOTCH1 [96]. The involvement of activated NOTCH1 in the pathogenesis of T-ALL was further demonstrated by animal models, in which expression of constitutively active forms of NOTCH1 were shown to induce T-cell tumorigenesis *in vivo* [125].

A broader role for NOTCH1 in T-cell leukemogenesis emerged when activating *NOTCH1* mutations were identified in more than 50% of T-ALL samples resulting in constitutive NOTCH signaling [28]. *NOTCH1* mutations mainly affect the heterodimerization (HD) domain and the C-terminal PEST domain. In addition, about 20% of T-ALL patients harbor mutations in both the HD and PEST domain of *NOTCH1* [28]. Finally, a rare but highly active group of alleles, the so-called juxtamembrane expansion (JME) mutations, result from internal duplication insertions in the extracellular juxtamembrane region of the receptor [126].

It was postulated that point mutations in the HD domain and JME alleles enhance the accessibility for proteolytic cleavage by γ-secretase, leading to ligand independent cleavage of NOTCH1 and release of ICN [28, 126]. Truncating mutations, as predominantly identified in the PEST domain, result in the removal of so-called Cdc phosphodegron domains (CPDs), which are normally involved in the degradation of ICN1 by the proteasome complex. PEST domain mutations therefore lead to the stabilization of ICN1. One of the proteins that bind to CPDs, thereby priming ICN for degradation, is the F-box protein FBXW7. FBXW7 is an E3-ubiquitin ligase that also regulates the half-life of other proteins including Cyclin E, cMYC, and cJUN [127].

Not surprisingly, mutations in this *FBXW7* gene were also identified as alternative or additional mechanism of NOTCH1 activation/stabilization in human T-ALL. Indeed, *FBXW7* point mutations were identified in 8–30% of T-ALL patients [128–130], frequently in association with NOTCH1 HD mutations [128–130].

Great interest exists in the inhibition of NOTCH1 signaling by GSIs as a potential therapeutic strategy in T-ALL. These small molecules interfere with the proteolytic cleavage of the receptor, inhibiting the release of ICN1 to the nucleus. GSIs induce growth arrest in some T-ALL cell lines and cause prolonged cell cycle arrest and apoptosis in primary T-ALL cells [28, 131]. However, despite the high prevalence of *NOTCH1* mutations and the presence of high levels of ICN1 in these tumors, some of these T-ALL cell lines failed to respond to NOTCH1 inhibition, suggesting primary resistance to GSI treatment [28]. Recently, it was shown that mutational loss of the tumor suppressor *PTEN* was associated with resistance towards NOTCH inhibition in T-ALL cell lines [115]. Importantly, although resistant for GSI treatment, PTEN mutant T-cell lines were highly sensitive for AKT inhibition, providing a rational for combined NOTCH1- and PI3K-AKT-directed therapeutic approaches in human T-ALL [32, 115]. Similarly, NOTCH1 regulates the NF-κB signaling pathway and inhibition of NOTCH signaling with GSIs can be synergistic with blocking the NF-κB with bortezomib [33].

However, the clinical development of GSIs has been hampered by the emergence of serious side effects, including severe gastrointestinal toxicity that results from conversion of intestinal

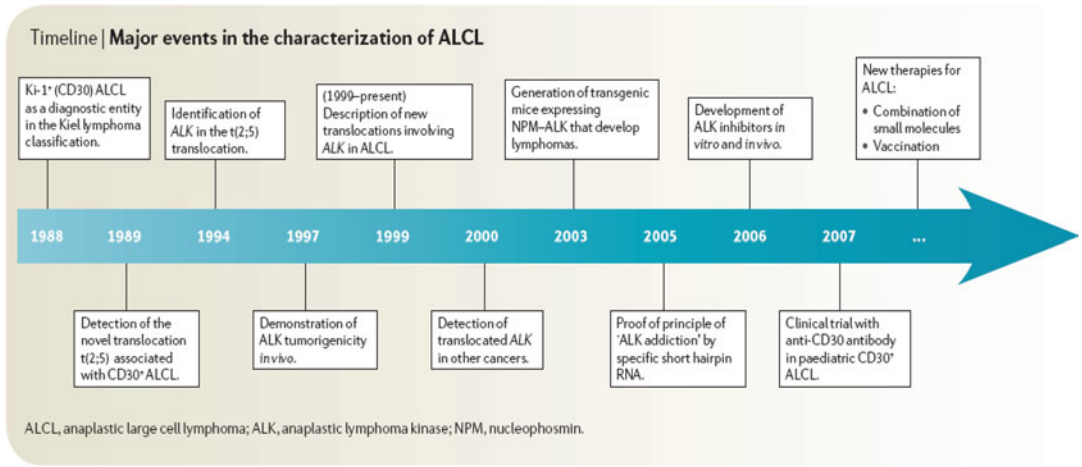

Fig. 11.7 Timeline of major events in the characterization of ALCL (reprinted from Chiarle et al. [138], with permission from Macmillan Publishers Ltd.)

crypt cells into goblet cells in the gut [132–134]. Notably, recent data suggested that inhibition of NOTCH1 signaling may reverse glucocorticoid resistance in some T-ALLs and that the combination of dexamethasone, a glucocorticoid extensively used in T-ALL treatment, and GSIs may ameliorate GSI-induced gut toxicity and provide a useful combination in the treatment of T-cell leukemias [29, 135]. Thus, NOTCH1 inhibition enhanced the effects of dexamethasone in glucocorticoid receptor autoupregulation and the activation of BIM-induced apoptosis [29].

Another clinically relevant downstream target of *NOTCH1* is the chemokine receptor *CCR7* which mediates the infiltration of CNS by leukemic lymphoblasts [136]. Therefore, pharmacological targeting of this chemokine receptor might reduce the risk of CNS relapse in T-ALL/T-LBL [136].

Overall, the identification of a multiplicity of molecular abnormalities in T-ALL has significantly improved our understanding of the mechanisms that contribute to the malignant transformation of T-cell precursors and opened the field for the development of specific targeted therapies blocking the activity of key genes and pathways required for the aberrant cell growth, proliferation, and survival of T-ALL/T-LBL lymphoblasts. In addition, further insights in the transcriptional networks regulated by the major T-cell oncogene *NOTCH1* revealed a variety of novel targets or treatment approaches that might be explored for T-ALL/T-LBL therapy, including the combined use of NOTCH inhibitors with PI3K-AKT pathway inhibitors [32, 115], anti-NF-κB drugs [33], and/or glucocorticoids [29, 135] or the targeting of the CCR7 receptor to prevent CNS relapse [136]. Hopefully, these novel treatment strategies will further improve T-ALL/T-LBL treatment outcome and reduce the therapy-related toxicities associated with intensive chemotherapy in T-ALL/T-LBL.

Anaplastic Large Cell Lymphoma in Children and Adolescents

Approximately 10% of NHLs that occur in children and adolescents are ALCL. First recognized in the 1980s [137], there have been significant advances in elucidating the distinct biological features of ALCL over the past 20 years (Fig. 11.7) [138]. There are two clinically distinct presentations of ALCL: a primary cutaneous form that presents exclusively in the skin and systemic ALCL [139]. Most cases of ALCL demonstrate TCR gene rearrangements, even when immunophenotypic analysis fails to demonstrate expression of T-cell antigens [140]. The systemic form of ALCL is most often characterized by

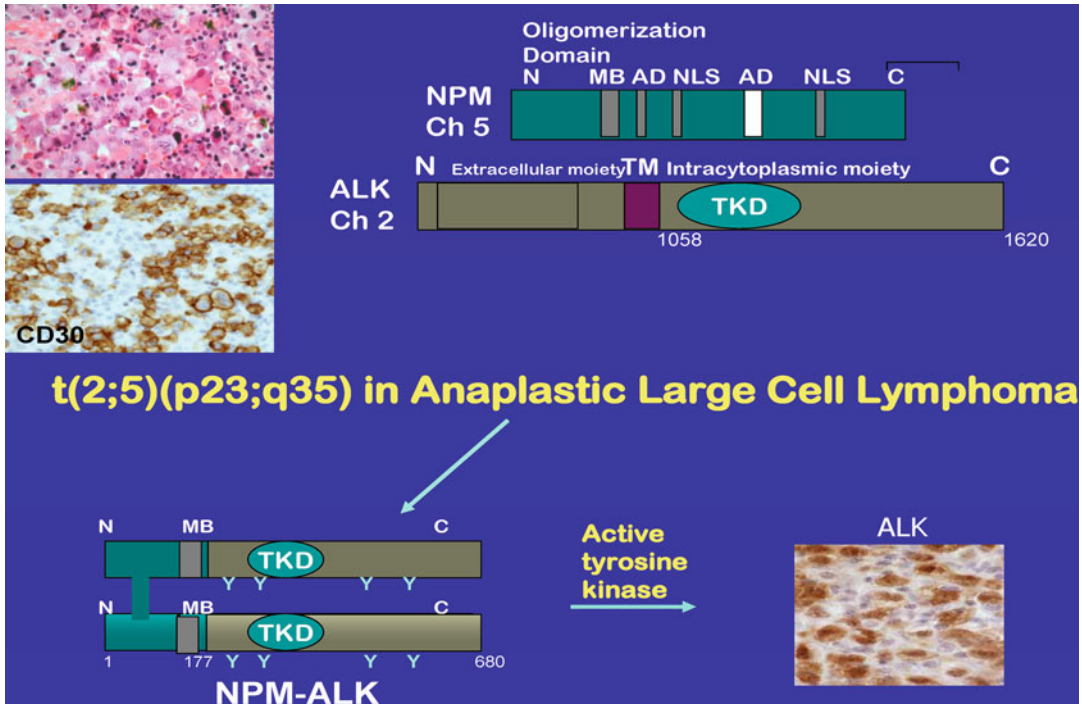

Fig. 11.8 Translocation of ALK gene on chromosome 2 with NPM gene on chromosome 5 in ALCL (adapted from Lim and Elenitoba-Johnson [180], with permission from The American Society for Biochemistry and Molecular Biology)

translocations of the *ALK* gene. Translocation of the *ALK* gene on chromosome 2q23 renders the disease ALK^+ (Fig. 11.8). The most common translocation in ALCL partners *ALK* with the nucleophosmin (*NPM*) gene on chromosome 5q35. Less common findings include translocation of *ALK* to partner genes on chromosomes 1, 2, 3, and 17 that also result in upregulation of *ALK* expression (Table 11.3) [141]. ALK^+ ALCL carries a significantly better prognosis than the ALK^- ALCL counterpart. These categorizations help determine risk stratification parameters and enable the implementation of appropriately different therapeutic approaches.

ALCLs are characterized by large, pleomorphic, multinucleated cells with eccentric horseshoe-shaped nuclei and abundant clear to basophilic cytoplasm with an area of eosinophilia near the nucleus (termed "hallmark cells") [142]. These "hallmark cells" may resemble Reed–Sternberg cells found in Hodgkin lymphoma (HL), although they tend to have less conspicuous nucleoli compared to Reed–Sternberg cells. Several morphologic variants of ALCL have been identified in the revised European American lymphoma (REAL) and WHO classifications [143]. These include the common variant (75%) composed primarily of hallmark cells, the lymphohistiocytic variant (10%) that has a large number of benign histiocytes admixed with neoplastic cells, and the small cell variant (10%) where small neoplastic cells predominate and only scattered hallmark cells are visualized. Other (<5%) less well-described variants include a sarcomatoid variant, signet ring variant, neutrophil rich variant, and giant cell variant [140].

The distribution of ALCL subtypes in children is different than in adults. More than 90% of childhood ALCL cases are ALK^+ [140], while approximately 60% of ALCL cases overall express *ALK* [144]. Primary cutaneous cases of ALCL are nearly always ALK^- and are quite uncommon in children [141]. Expression of *ALK* is not entirely unique to ALCL, as it is a gene

Table 11.3 Recurrent chromosomal translocations involving ALK in cancers

Chromosomal translocation	Partner protein	Frequency (%)	Fusion protein (KDa)	Cellular localization	Type of tumor	References
t(2;5)(p23;q35)	Nucleophosmin (MPM)	75–80	NPM-ALK (80)	Nucleus, nucleolus, and cytoplasm	ALK$^+$ ALCL and ALK$^+$ DLBCL	[224–227]
t(1;2)(q25;p23)	Tropomyosin 3 (TPM3)	12–18	TPM3-ALK (104)	Cytoplasm	ALK$^+$ ALCL and IMT	[228–230]
t(2;3)(p23;q21)	TRK-fused gene (TFG)	2	TFG-ALK (113, 97, 85)	Cytoplasm	ALK$^+$ ALCL	[231, 232]
inv(2)(p23;q35)	ATIC	2	ATIC-ALK (96)	Cytoplasm	ALK$^+$ ALCL and IMT	[233–235]
t(2;17)(p23;q23)	Clathrin heavy chain-like 1 (CLTC1)	2	CLTC1-AKL (250)	Granular cytoplasmic	ALK$^+$ ALCL, IMT and ALK$^+$ DLBCL	[236–238]
t(2;X)(p23;q11-12)	Moesin (MSN)	<1	MSN-ALK (125)	Cell membrane associated	ALK$^+$ ALCL	[239, 240]
t(2;19)(p23;p13)	Tropomyosin 4 (TPM4)	<1	TPM4-ALK (95–105)	Cytoplasm	ALK$^+$ ALCL and IMT	[229, 241]
t(2;17)(p23;q25)	ALO17	<1	ALO17-ALK (ND)	Cytoplasm	ALK$^+$ ALCL	[242]
t(2l2)(p23;q13) or inv(2)(p23;q11-13)	RAN binding protein 2 (RANBP2)	<1	RANBP2-ALK (160)	Periphery of the nucleus	IMT	[243]
t(2;22)(p23;q11.2)	Non-muscle myosin heavy chain (MYH9)	<1	MYH9-ALK (220)	Cytoplasm	ALK$^+$ ALCL	[244]
t(2;11;2)(p23;p15;q31)	Cysteinyl-tRNA synthetase (CARS)	<1	CARS-ALK (130)	Unknown	IMT	[242, 245]
ins(3′ALK)(4q22-24)	Unknown	<1	Unknown	Granular cytoplasmic	ALK$^+$ DLBCL	[246]
t(2;4)(p23;q21)	SEC31 homologue A (*S. cerevisiae*) (SEC31L1)	<1	SEC31L1-ALK (ND)	Cytoplasm	IMT	[247]
inv(2)(p21;p23)	Echinoderm microtubule-associated protein-like 4 (EML4)	6	EML4-ALK (ND)	Unknown	NSCLC	[248]

Reprinted from Chiarle et al. [138], with permission from Macmillan Publishers Ltd.
ALCL anaplastic large cell lymphoma; *ALK* anaplastic lymphoma kinase; *ALO17* ALK lymphoma oligomerization partner on chromosome 17; *ATIC* 5-aminoimidazole-4-carboxamide ribonucleotide formyltransferase/IMP cyclohydrolase; *DLBCL* diffuse large B-cell lymphoma; *IMT* inflammatory myofibroblastic tumors; *ND* not determined; *NSCLC* non-small-cell lung cancer

normally involved in neuronal development and is rarely seen in cases of diffuse large B-cell lymphoma (DLBCL) and also in inflammatory myofibroblastic tumors [145].

Children tend to present with advanced stage III/IV ALCL at diagnosis [146]. Around 40–60% of patients with systemic ALCL present with B symptoms and have extranodal disease, most commonly involving the skin (20–25%), bone, and soft tissue, and commonly in association with nodal disease [147]. This contrasts with primary cutaneous ALCL, which although extranodal, is limited solely to the skin. Skin lesions usually present as solitary or localized nodules; however multifocal skin involvement occurs in 15–20% of patients [1, 2]. Involvement of the bone marrow occurs in less than 10% of patients [144], and CNS involvement is less common in ALCL than in other forms of childhood NHL such as BL and LBL, occurring in less than 5% of patients [148].

Risk stratification is ultimately important in the determination of the treatment of ALCL. Optimal therapeutic approaches for limited disease ALCL has yet to be established, as both B-NHL intensive therapy and T-ALL protocols have been used with similar efficacies. EFS has been reported to be as high as 100% for children with localized ALCL (stage I/stage II resected) in the NHL-BFM90 trial with 2 months of chemotherapy including dexamethasone, ifosfamide, MTX, cytarabine, etoposide, and prophylactic IT therapy [149]. St. Jude Children's Research Hospital reported a 75% EFS on a small number of children with localized CD30 positive large cell lymphoma (presumably ALCL) treated with three courses of CHOP (cyclophosphamide, doxorubicin, vincristine, and prednisone), either with or without maintenance therapy (6-mercaptopurine plus MTX) [150].

Treatment of advanced stage ALCL in children has evolved over the past two decades. Different strategies, including B-NHL intensive protocols and LSA_2-L_2-type therapies, have achieved EFS rates ranging between 65 and 75% (Table 11.4) [149, 151–155]. The backbone of combination doxorubcin, prednisone, and vincristine (APO) has been investigated in multiple trials over the past 15 years. Pediatric Oncology Group (POG)-9315 examined the utility of adding intermediate-dose MTX and high-dose cytarabine to the backbone APO regimen vs. standard APO alone; however there was insufficient power in the study to detect a difference between the two arms and those patients receiving MTX and cytarabine experienced greater toxicity. Children treated on the backbone APO arm had a 2-year EFS of 75.1% [152]. More recently, the COG has examined the addition of weekly vinblastine to the APO regimen based upon French data showing the remarkable overall response rate (ORR) of patients (10 out of 12) with relapsed ALCL to weekly vinblastine [156]. However in a recent report of the results from the COG study, the addition of vinblastine had no statistically significant improvement on the EFS or OS and was associated with increased myelosuppression. The overall 2-year EFS for the study was 77% [157]. Results from the international trial ALCL99 based upon the European approach of utilizing multi-agent intensive B-NHL-like therapy (built upon the BFM90 protocol) were recently reported. The study revealed an improvement in safety in utilizing a less toxic regimen including administration of high-dose MTX without IT chemotherapy and reported a 2-year EFS of 74% [158].

Until the ALCL99 trial, cases of CNS negative ALCL had been treated with prophylactic IT chemotherapy. With the recent success in preventing CNS relapse without the use of IT chemotherapy, the question arises whether a reduction in the number of high-dose MTX administrations can be employed. CRT in doses of 18–24 Gy in addition to high-dose MTX and/or Cytarabine and IT medicines has been reserved for cases of those rare patients with overt CNS disease [149, 151].

Several prognostic parameters have been identified in children with advanced disease ALCL. Some of the poor-risk clinical prognostic factors that have been identified include visceral organ involvement (liver, lung, spleen), mediastinal involvement, elevated lactate dehydrogenase (LDH), and disseminated skin disease (Fig. 11.9) [151, 159, 160]. More recently, correlation between tumor biology and treatment failure has become extremely important. Presence of MRD

Table 11.4 Advanced anaplastic large cell lymphoma in children

	BFM [149]	POG [152]	SFOP [151]	St. Jude [150]	MSKCC [166]	CCG [153]	EICNHL [159]	EICNHL [158]
Patients (*N*)	89	67	82	18	19	86	225	352
Protocol	NHL-BFM 90	POG 9315	HM89-91	CHOP-based	LSA_2L_2, LSA_4	CCG-5941	BFM, SFOP, UKCCSG	Modified NHL-BFM 90
Duration (months)	2–5	12	7–8	6–18	14–36	12	2–8	4–12
EFS (Est) 2–5 year	76%	73%	66%	57%	56%	68%	69%	75%
OS 2–5 years	NR	93%	83%	84%	84%	80%	81%	94%

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EFS event-free survival; *Est* estimate; *OS* overall survival

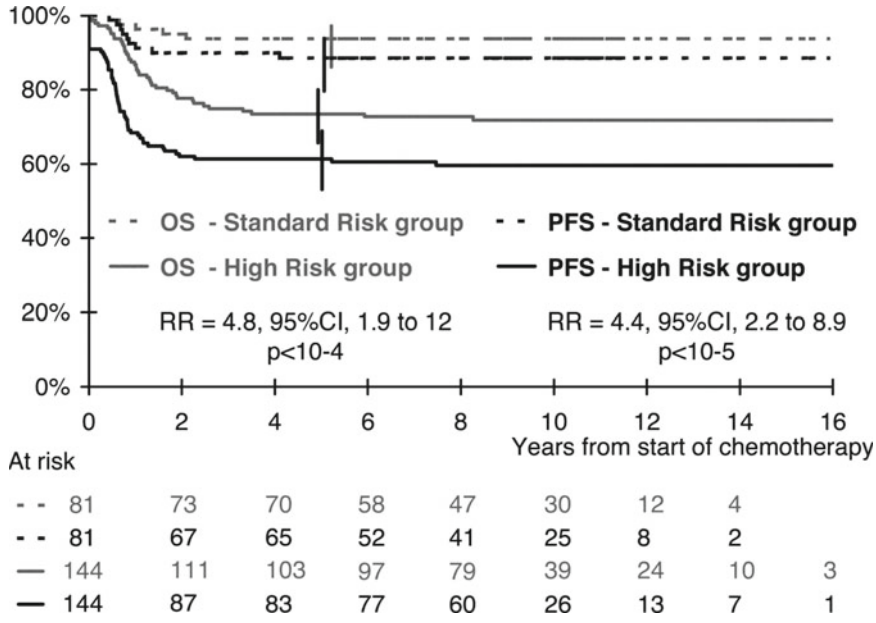

Fig. 11.9 OS and PFS according to risk group. Standard risk group indicates no risk factor (i.e., no mediastinal involvement and no lung, spleen, or liver involvement, and no skin lesion). High-risk group, at least 1 risk factor, mediastinal involvement, visceral involvement, or skin lesion. This research was originally published in *Blood* [159]. © American Society of Hematology

as detected by PCR analysis of the *NPM-ALK* transcript in the bone marrow and peripheral blood was associated with a significant increase in cumulative incidence of relapse in ALCL, 50% for PCR positive vs. 15% for negative (Fig. 11.10) [161]. Meanwhile, the presence of anti-*ALK* antibodies is inversely correlated to tumor dissemination and the risk of relapse in *ALK*$^+$ ALCL and supports the use of *ALK* as an important potential immunotherapeutic target [162]. Additionally, analysis of the recent ALCL99 international trial revealed that two of the less common morphologic subtypes of ALCL, small cell and lymphohistiocytic, were significantly associated with a high risk of treatment failure, independent of clinical risk factors [163]. Ultimately, the continued development in the ability to predict those patients at higher risk for relapse will enable an intensification of front-line therapy and potentially improve outcomes.

Chemosensitivity at the time of relapse is a hallmark feature of childhood ALCL and has rendered salvage strategies for ALCL generally effective [164, 165]. Relapses in ALCL tend to occur later than in other histologic subtypes of childhood NHL [166]. The clinical behavior after relapse has been variable with some patients developing rapidly progressive disease and others having an indolent, waxing and waning course [167]. These differences have made uniform treatment approaches difficult to establish. In analyzing a series of three clinical trials in France over two decades, therapeutic intervention for relapse varied widely from single agent Vinblastine, to multi-agent chemotherapy, to fully ablative chemotherapy with both autoSCT and alloSCT. Higher risk for treatment failure included earlier relapse and more intensive initial treatment. Three-year risk DFS was not significantly different in patients who underwent ablative SCT in CR2 vs. those treated with chemotherapy alone [156]. However, more recent reports of alloSCT for relapsed and refractory ALCL have demonstrated encouraging results including a 3-year EFS of 75% for the larger series of 20 patients (Fig. 11.11) [168, 169].

Currently, new treatment strategies are focusing on determining the utility of targeted agents

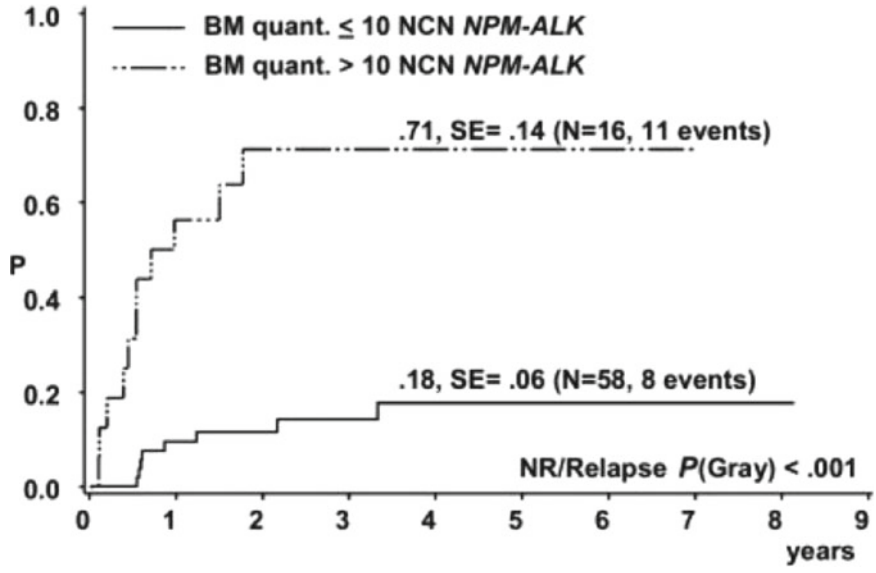

Fig. 11.10 Outcome of ALCL patients according to quantitative PCR results for *NPM-ALK* in bone marrow. Cumulative incidence of relapse of the 74 patients with either a negative qualitative BM PCR or a positive qualitative BM PCR using quantitative PCR results and a *NPM-ALK* cutoff copy number of $10/10^4$ copies *ABL* (NCN). This research was originally published in *Blood* [161]. © American Society of Hematology

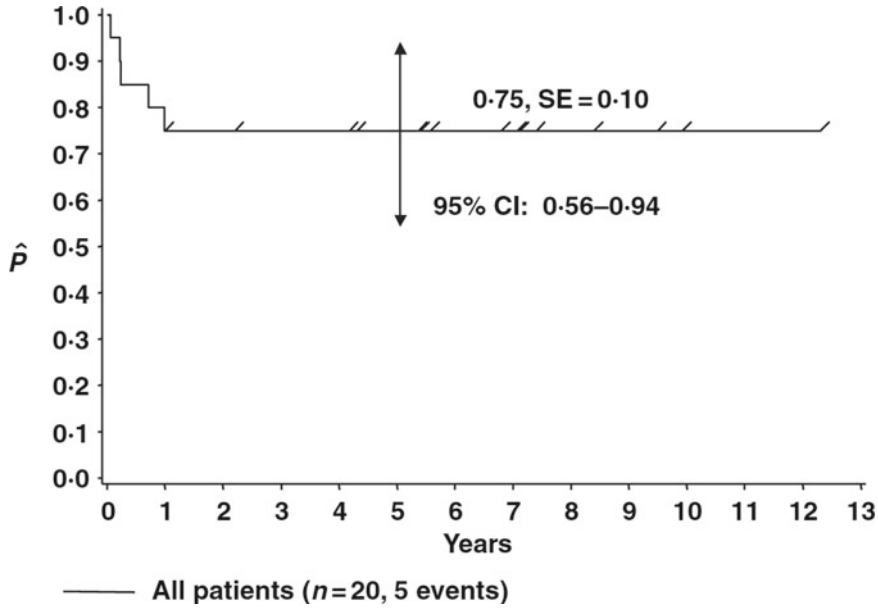

Fig. 11.11 EFS estimate for the 20 patients with anaplastic large cell lymphoma-relapse treated by allogeneic hematopoietic stem cell transplantation (reprinted from Woessmann et al. [169], with permission from Wiley-Blackwell Publishing)

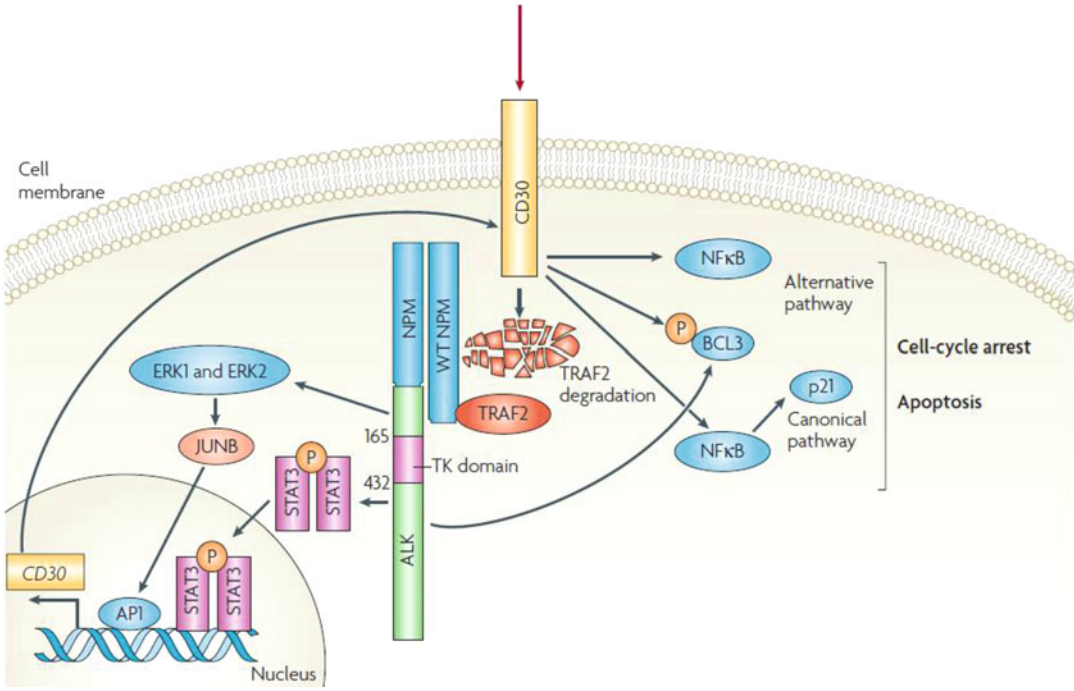

Fig. 11.12 ALK and CD30 signaling. In anaplastic large cell lymphoma (ALCL), CD30 expression is controlled by anaplastic lymphoma kinase (ALK) activity through the phosphorylation of signal transducer and activator of transcription 3 (STAT3) and the extracellular signal-regulated kinase 1 (ERK1)- and ERK2-mediated upregulation of JUNB protein levels. Phosphorylated STAT3 and activated AP1 complexes containing JUNB cooperate to enhance *CD30* transcription. The nucleophosmin (NPM)–ALK fusion protein impedes full CD30 signaling and nuclear factor κB (NFκB) activation by titrating tumor necrosis factor receptor-associated factor 2 (TRAF2) away from CD30 through dimerization with wild-type (WT) NPM. CD30 engagement results in TRAF2 degradation and BCL3 phosphorylation. The effect of CD30 engagement in ALCL cells is the activation of both the canonical and alternative NFκB pathways, which result in apoptosis and p21-mediated cell-cycle arrest. Clinical trials are currently using specific antibodies directed against CD30 (*red arrow*) in ALCL109. *TK* tyrosine kinase (reprinted from Chiarle et al. [138], with permission from Macmillan Publishers Ltd.)

as well as the optimal risk stratification that would determine using alloSCT in frontline therapy. CD30 antigen is expressed in close to 100% of all childhood and adolescent ALCL; this expression is controlled by *ALK* (Fig. 11.12). In phase I/II trials, one partial response and one CR have been achieved with SGN-30 monotherapy in heavily pretreated patients with relapsed and refractory ALCL [170, 171]. More recently, SGN-35, another monoclonal antibody targeting the CD30 antigen, has met even greater success than its predecessor. Two separate phase I trials have examined the role of SGN-35 monotherapy in patients with refractory/recurrent $CD30^+$ lymphomas including cases of both ALCL and HL. At higher dose ranges of drug, preliminary data in one trial revealed that 7 of 8 evaluable patients achieved CR. In the other trial, also at the higher dose ranges of drug, 7 of 28 evaluable patients achieved CR with an ORR of 46% [172, 173]. The impressive response to monotherapy in heavily pretreated patients offers exciting hope that incorporating SGN-35 into combination therapy will provide promise for better results with frontline therapy.

Advances in the study of the biological characteristics of ALCL have also led to the development of novel therapeutic agents. Potential developmental therapeutic strategies include targeting the *ALK* protein with both small molecule inhibition as well as directed antibodies. The *ALK* inhibitor TAE684 has proven effective with

in vitro and *in vivo* inhibition of *ALK*$^+$ ALCL. In separate mouse models the drug was able to achieve prevention of tumor development as well as regression of pre-induced tumor [174]. The aforementioned evidence showing a strong correlation with circulating anti-*ALK* antibodies and a lower risk for relapse has led to investigations in vaccination strategies stimulated by the *ALK* antigen [175]. Somatic mutations in ALCL are rare. Monoallelic and biallelic mutations of the perforin (*PRF1*) gene and sonic hedgehog (*SHH*) have been reported in some cases of childhood lymphomas. Direct sequencing identified 6 different mutations in 12 patients (27.3%) of 44 patients with t(2;5)+ALCL. The incidence of *PRF1* mutations was found to be significantly higher in patients with ALCL compared with 400 control subjects, among whom only heterozygous A91V was observed in 41 subjects (10.2%) (chi-square test, 10.9; $P<0.01$) [176]. *PRF1* mutations have been described in other NHLs and are thought to result in defective perforin-mediated cytotoxicity due to abnormal conformational changes induced by the A91V mutation [177]. Amplification of *SHH* gene in a subset of *ALK* positive ALCL [178] has been shown to lead to deregulation of the *SHH* signaling pathway. While genomic studies were essential in identifying the characteristic upregulation of the *ALK* protein in ALCL, proteomic studies of ALCL have been instrumental in understanding the importance of the *ALK* gene and its associated network of proteins (Fig. 11.13a, b) [179, 180]. Most recently, unraveling of the proteomic signature of the *NPM/ALK* fusion gene identified cellular changes affecting cell proliferation, ribosome synthesis, survival, apoptosis evasion, angiogenesis, and cytoarchitectural organization [179]. Further investigation showed loss of cell adhesion as a consequence of *NPM/ALK* expression in a kinase-dependent manner, and sensitivity of *NPM/ALK*-positive ALCLs to inhibition of the *RAS*, p42/44ERK, and FRAP/mTOR signaling pathways [179]. Understanding the effects of *NPM/ALK* alteration on a diverse array of cellular pathways offers novel insights into *NPM/ALK*-positive ALCL pathobiology. Other proteomic studies have demonstrated the constitutive expression of CD25 in pediatric ALCL and have led to *in vitro* investigations of the anti-CD25 agent, denileukin diftitox, as a novel therapeutic approach [181, 182]. Furthermore, the identification of other important downstream cellular pathways interconnected with *ALK* has led to studies examining the utility of disrupting *ALK*-associated pathways in an attempt to prevent tumorigenesis. Heat shock protein 90 (*Hsp-90*) and the PI3K/Akt apoptosis pathway have both demonstrated interactions with the *ALK* protein network. *In vitro* studies targeting *Hsp-90* resulted in increased degradation of *NPM-ALK* and subsequent apoptosis in ALCL cell lines [183], while PI3K/Akt negative mice injected with *NPM/ALK*$^+$ cells showed significantly impaired tumor forming capacity [184]. Altogether, advances in our understanding of the genomic and proteomic characteristics of ALCL have enabled an expanded approach to therapeutic targeting of developmental strategies. Combining new and less toxic therapies offers an exciting opportunity to enhance both the efficacy and safety of therapies for future patients.

Other Peripheral T-Cell Lymphomas in Children and Adolescents

PTCLs other than ALCLs are composed of a diverse group of rare disease entities. After ALCL, PTCL-not otherwise specified (nos) makes up the second largest type of PTCL. In children, PTCL-nos accounts for only approximately 1% of all cases of NHL [185]. In contrast, it represents around 4% of NHL in adults [186]. It is important to remember though, that the incidence of PTCL varies based on geographical and ethnic differences; for example, there is a distinctly higher prevalence of PTCL in Asia [186]. While the etiology of certain subtypes of PTCL is well described (i.e., human T-cell lymphotropic virus [HTLV] in adult T-cell leukemia/lymphoma and Epstein–Barr virus [EBV] in the EBV T-cell lymphoproliferative [LPD]), for the most part the etiology of this diverse group of diseases has yet to be determined [3].

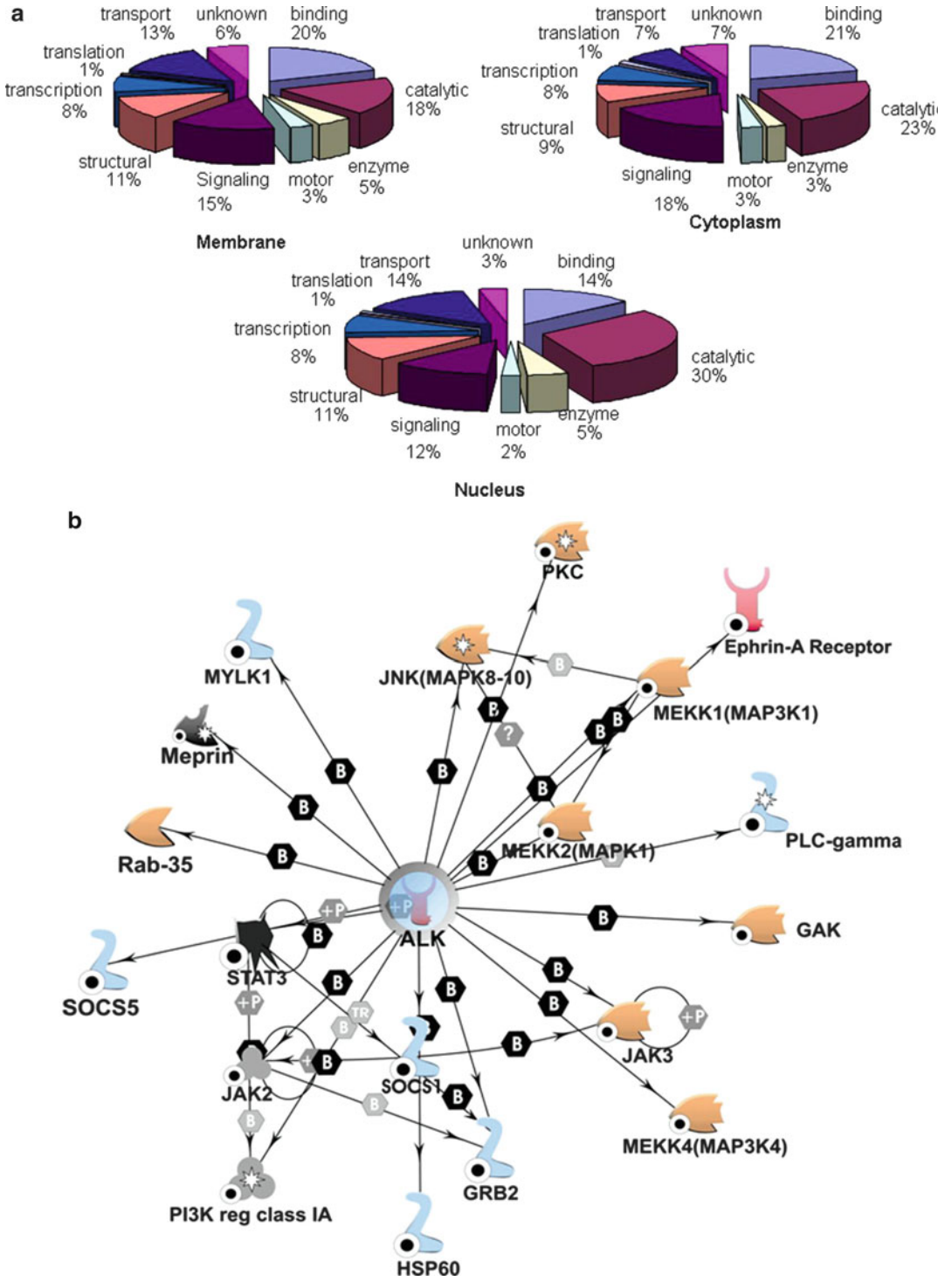

Fig. 11.13 (**a**) Functional categories of proteins expressed in the membrane, cytoplasmic, and nuclear fraction of ALCL. GoMiner analysis of proteins identified in the membrane, cytoplasmic, and nuclear fractions reveals proteins from diverse functional categories. (**b**) Proteins identified within the NPM/ALK protein network. The proteins identified within the NPM/ALK immunocomplex are visualized using GeneGO software analysis. *reg* regulated; *PKC* protein kinase C; *GAK* cyclin G-associated kinase (reprinted from Lim and Elenitoba-Johnson [180], with permission from The American Society for Biochemistry and Molecular Biology)

Table 11.5 WHO 2008 classification of precursor and mature T/NK-cell neoplasms

Leukemic or disseminated
T lymphoblastic leukemia/lymphoma
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorders of NK cells
Aggressive NK-cell leukemia
Adult T-cell lymphoma/leukemia (HTLV1-positive)
Systemic Epstein–Barr virus (EBV)-positive T-cell lymphoproliferative disorders of childhood
Extranodal
Extranodal NK/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma
Hepatosplenic T-cell lymphoma
Extranodal-cutaneous
Mycosis fungoides
Sezary syndrome
Primary cutaneous $CD30^+$ lymphoproliferative disorders
Primary cutaneous anaplastic large cell lymphoma
Lymphomatoid papulosis
Subcutaneous panniculitis-like T-cell lymphoma
Primary cutaneous gamma-delta T-cell lymphoma
Primary cutaneous aggressive epidermotropic $CD8^+$ cytotoxic lymphoma
Nodal
Angioimmunoblastic T-cell lymphoma
Anaplastic large cell lymphoma, ALK-positive
Anaplastic large cell lymphoma, ALK-negative
Primary cutaneous small/medium $CD4^+$ T-cell lymphoma

Based on data from refs. [1, 2]

The other entities of PTCL are too numerous to discuss each in great detail, but are listed in Table 11.5. The 2008 WHO Classification of Lymphoid Neoplasms has subdivided PTCLs into four groups based upon their mode of clinical presentation: leukemic/disseminated, extranodal, extranodal-cutaneous, and nodal. Examples of the leukemic/disseminated types include the HTLV-1 positive adult T-cell lymphoma/leukemia and systemic EBV positive T-cell LPD of childhood. The extranodal variety of PTCL includes extranodal NK/T-cell lymphoma, enteropathy-associated T-cell lymphoma, and hepatosplenic lymphoma. The extranodal-cutaneous forms include Mycosis Fungoides/Sezary syndrome, primary cutaneous $CD30^+$ LPD (discussed in more detail in the ALCL section), subcutaneous panniculitis-like T-cell lymphoma, and primary cutaneous γδ T-cell lymphoma. The nodal sub group includes ALCL, angioimmunoblastic T-cell lymphoma, and PTCL-nos, previously referred to as PTCL-u [139].

The biological characteristics of PTCL-nos also exhibit diversity. It has been challenging to identify the normal counterpart T cells that correlate with the cellular origin of disease for PTCL-nos. A variety of immunophenotypic changes have been observed across different stages of T-cell differentiation with cells expressing different combinations of pan-T-cell antigens as well as markers of both cytotoxic and activated T-cell subtypes [187]. Similarly, although several different cytogenetic changes have been observed in cases of PTCL-u, a specific pattern that correlates to clinically meaningful consequences has yet to be established [188]. In fact, ALCL is the only T-cell lymphoma that is characterized by a consistently recurring genetic abnormality in the t2;5 translocation [189]. Furthermore, although clonal gene rearrangements of the TCR are often seen in cases of PTCL-u, these molecular changes vary and none serve to represent a characteristic pattern [3].

Some recent observations in the biological behavior of PTCL have opened the door to some exciting scientific investigations. Gene array analysis of PTCL-u specimens has linked the reduced expression of *NF-κB* genes with shorter survival [190]. While further studies are required to understand the precise relationship between the *NF-κB* pathway and PTCL-u tumorigenesis, this data offers an excellent opportunity to improve our understanding of disease progression as well as discover a target for developmental therapeutics. Similarly, another study was able to separate PTCL-u into three subgroups based upon microarray-based genomic findings. These three groups included one characterized by the expression of cyclin D2, another with the overexpression of *NF-κB1* and *Bcl-2* genes, and the third marked by overexpression of genes involved in the interferon/JAK/STAT pathway [191]. Again, while further investigations are required

to unravel a deeper understanding of these pathways and how they are involved in lymphomagenesis, these studies have identified novel and potentially important biological observations in PTCL.

The clinical presentations of PTCL are as varied as the biological characteristics. Most patients present with either generalized lymphadenopathy (commonly in the cervical region) or extranodal disease. The extranodal presentation often involves the liver, spleen, skin, and bone marrow. The majority of patients have advanced stage disease at diagnosis and exhibit systemic constitutional B symptoms such as fevers, night sweats, and/or weight loss. LDH is often elevated and there may or may not be abnormalities appreciated on the CBC. Often times patients are found to have symptoms associated with increased cytokine production from the abnormal T cells and can even present with the overt hyperinflammatory signs of a hemophagocytic syndrome [3].

Unfortunately, treatment strategies employed over the years for PTCL have been as varied as their clinical and pathological findings. It has been extremely challenging to develop and establish effective treatment regimens because the clinical experience in pediatric PTCL has been sparse and individual studies have been hampered by too few patients. The largest cohorts of pediatric PTCL patients have recently been reported from the United States of America (USA) and the United Kingdom (UK).

The COG analyzed 20 pediatric patients identified over a 9-year period. The cohort included mostly patients with PTCL-u; however there were also patients with extranodal NK/T-cell lymphoma nasal type, subcutaneous panniculitis-like T-cell lymphoma, and enteropathy-type T-cell lymphoma. Treatment choice was differentiated based upon clinical staging. Patients with advanced stage III/IV disease were treated with a regimen of doxorubicin, prednisone, vincristine, mercaptopurine, and MTX ± alternating therapy with high-dose cytarabine and intermediate-dose MTX. Patients with localized stage I/II disease were treated with CHOP. Of patients with localized disease, 2 relapsed and 9 of 10 survived. Of patients with advanced stage disease, 6 relapsed and 5 of 10 survived. These results are markedly better than most studies analyzing adults with PTCL. However, while CHOP-like therapy seems adequate for patients with localized disease, the OS for patients with advanced stage disease was only 50%, leaving plenty of room for improvement [192].

The experience in the UK was quite similar to that of the COG in the USA. The UK study analyzed 25 cases of PTCL in children and adolescents over a 20-year period. They observed a similar distribution of PTCL subtypes with 68% of patients having PTCL-u, the remainder of cases were angiocentric PTCL, angioimmunoblastic T-cell lymphoma, and subcutaneous panniculitis-like T-cell lymphoma. In this retrospective analysis, patients were treated either with B-NHL CHOP-like regimens or with T-ALL type of treatment strategies. Among children with PTCL-u, 9 of 12 survived with T-ALL therapy, while only 1 of 5 that received B-NHL therapy survived. Similar to the COG results, when analyzed based upon extent of disease, the majority of patients (9 of 12) with localized stage I/II disease survived, while only 6 of 12 children with advanced stage disease survived. The authors concluded that children with PTCL-u should be treated with T-ALL-like therapy; however it is still apparent that a large percentage of children with advanced stage disease do not survive [185].

Outcomes for adults with PTCL have been even worse. Treatment strategies have varied widely, yet 5-year OS in adult studies has ranged from 25 to 45% [3, 193–195]. Conventional chemotherapy combinations used in adults have most frequently included CHOP-like therapy; however there have also been attempts to incorporate cytarabine, cisplatin, and etoposide without any improvement in survival rates. With the poor outcomes from conventional chemotherapy, the use of high-dose chemotherapy with both autoSCT and alloSCT has also been explored.

High-dose chemotherapy with autoSCT has been attempted as both salvage and front-line therapy in PTCL. In the setting of refractory or recurrent disease, OS after autoSCT has been

reported around 33% [196]. Some studies report higher OS rates ranging between 39 and 48%; however their cohorts included cases of ALCL which typically do well with autoSCT for salvage therapy. When analyzed based upon histologic subtype, the cases of PTCL had OS closer to 30% in those same studies [197]. Attempts to treat PTCL with front-line autoSCT have yielded slightly better results; however the biggest obstacle to achieving better outcomes was the inability to attain remission in significant numbers of patients. A large study performed in Italy for patients with high-risk PTCL receiving autoSCT as up-front therapy reported long-term OS rates of 39%. However, a number of patients progressed before autoSCT and never received the therapy. Of the patients that did get high-dose chemo and autoSCT, 12-year DFS rate was 55% [198].

Many groups have also attempted alloSCT for PTCL. This strategy provides the advantage of infusing lymphoma-free grafts and potential for a graft vs. lymphoma effect. Studies have demonstrated a lower risk of relapse in patients receiving alloSCT (in comparison to autoSCT); however the high rates of transplant-related mortality with fully ablative conditioning regimens have offset any survival advantages [199]. The Italian group has recently reported on the role of alloSCT with reduced intensity conditioning regimens. In a pilot study of 17 patients with refractory and recurrent disease (8 of whom relapsed after prior autoSCT), a 3-year progression-free survival of 64% was achieved, with only 1 of 17 patients suffering from transplant-related mortality [200]. This study offers promising data for a disease that has been notoriously difficult to treat for many years.

Pediatric studies have shown that patients with advanced stage III/IV disease have markedly worse outcomes than those with localized stage I/II disease [185, 192]. In adults, the International Prognostic Index (IPI) has commonly been used for risk stratification. The IPI incorporates high-risk features such as advanced stage disease, LDH level greater than twice normal, elderly patient age, multifocal extranodal involvement of disease, and poor performance status. A Canadian study demonstrated the validity of the IPI in adult patients with PTCL-u, showing that of 117 patients, those with an IPI score of 0–1 (30% of the cohort) had a 5-year OS of 64%, while those with an IPI score >2 (70% of the cohort) had an OS of 30% [195]. The Italian group has established the Prognostic Index for PTCL-u (PIT) model based upon principles from the IPI and results from a series of nearly 400 patients. Using four clinical variables, age, performance status, LDH level, and bone marrow involvement, they were able to identify prognostic groups. Groups 1 and 2 had zero or one adverse factor and 5-year OS rates of 62% and 53%, respectively. Groups 3 and 4 had two or more than two adverse factors and OS rates of 33% and 18%, respectively [201]. In application to pediatric patients, certainly they will not carry the adverse factor of elderly age status, but indicators of advanced stage disease like elevated LDH and bone marrow involvement will portend for a worse prognosis.

With the overall poor outcomes in adult patients with PTCL and pediatric patients with advanced stage PTCL, advances in therapeutic strategies are desperately needed. New agents in investigation for PTCL include a wide array of agents from the following pharmacologic categories: nucleoside analogs, histone deacetylase inhibitors, anti-angiogenesis agents, folate inhibitors, proteasome inhibitors, and monoclonal antibodies. Of the nucleoside analogs, pentostatin and gemcitabine have shown the most promise. A single institution study demonstrated an ORR to gemcitabine in refractory/recurrent disease to be 60%; however there were only ten patients evaluated [202]. Currently gemcitabine is being investigated in combination with other agents against a variety of lymphomas. Nelarabine, on the other hand, achieved an ORR of only 10.5% and also exhibited marked toxicity [203]. The histone deacetylase inhibitor, depsipeptide, induced an ORR of 26% in data from a phase II trial [204]. Anti-angiogenesis agents like bevacizumab have been utilized specifically in angioimmunoblastic T-cell lymphoma and there are some case reports of achieving CR in refractory/recurrent cases [205, 206]. The new anti-folate agent Pralatrexate has shown promise

in phase I/II trials with an ORR of 47% in 26 patients with T-cell lymphoma, many of whom had PTCL [207]. Investigations were expanded to a multicenter trial enrolling over 100 patients with PTCL, with interim data showing ORR of 29% in 65 patients, with 11% of total patients achieving CR [208]. Combining proteasome inhibitor, bortezomib, with liposomal doxorubicin has proven safe and effective for advanced stage hematologic malignancies [209]. Proteasome inhibitors are known to promote apoptosis and the anti-proliferative properties via inhibition of the NF-κB pathway. Bortezomib thus provides an attractive mechanism of action in PTCL with recent biology studies demonstrating an overexpression of *NF-κB1* genes in certain subgroups of PTCL. It has been investigated in refractory and relapsed cutaneous T-cell lymphomas, achieving an ORR of 67% as single-agent therapy. Although the majority of cases in that trial were *Mycoses Fungoides*, which is characteristically unique in comparison to other forms of PTCL, there were two patients with PTCL-u in that study, one of whom achieved response [210]. Currently there are studies examining the role of bortezomib in combination with other therapies for PTCL as front-line therapy [211].

The development of monoclonal antibodies has fostered much progress in the treatment of pediatric lymphomas in the past decade. In PTCL there has been much interest in incorporating monoclonal antibodies into combination therapeutic regimens. Alemtuzumab is a humanized monoclonal antibody that targets CD52, an antigen expressed on nearly all lymphocytes. It has been studied as a single agent in refractory/recurrent cases of PTCL, achieving a 36% ORR in a pilot study of 14 patients. However, there were excessive infectious complications experienced in the study with five patients suffering from treatment-related mortality [212]. A more recent study examined the role of alemtuzumab in combination with CHOP chemotherapy as front-line therapy. This experience revealed tolerable rates of toxicity and 1-year EFS of 41% [213]. Other monoclonal antibodies have been explored in the setting of cutaneous T-cell lymphomas and their utility in other forms of PTCL remains to be elucidated. They include the anti-CD4 antibody zanolimumab, as well as daclizumab and denileukin diftitox, two antibodies targeting the CD25 antigen, which is a form of the human IL-2 receptor [214, 215].

Rare T-Cell Lymphomas in Children and Young Adolescents

Hepatosplenic Gamma Delta T-Cell Lymphoma

This is a very rare and aggressive peripheral T-cell neoplasm that is characterized by involvement of the liver, spleen, and bone marrow. It is a disease of young adults with a distinct male predominance. Patients present with marked hepatosplenomegaly without lymphadenopathy. Up to 20% of cases arise in the setting of chronic immune suppression, most commonly in the setting of solid organ transplantation or prolonged antigenic stimulation as in inflammatory bowel disease after exposure to azathioprine and infliximab. More recently, EBV-negative T-cell lymphomas with features consistent with hepatosplenic T-cell lymphomas have been reported in patients receiving infliximab for inflammatory bowel disease [216]. Molecular studies consistently show isochromosome 7q often in conjunction with trisomy 8. The cells have rearranged TCR genes. Gene expression profiling of γ/δ T-cell lymphoma [217] revealed that genes of NK-cell associated molecules such as killer cell immunoglobulin-like receptor genes and killer cell lectin-like receptors were found to be overexpressed relative to other PTCL with α/β phenotype. Gene ontology analysis of differentially expressed genes show enrichment of those involved in cellular defense response, signal transduction activity, receptor activity, transmembrane receptor activity, and immunoglobulin-G binding.

EBV Positive T-Cell Lymphoproliferative Disorders

In the 2008 WHO classification two new major types of EBV-associated T-cell LPDs affecting the pediatric population have been incorporated:

systemic EBV-positive T-cell LPD of childhood and Hydroa vacciniforme-like lymphoma. Both of them occur predominantly in Asians and in Native Americans from Central and South America and Mexico.

Systemic EBV-Positive T-Cell Lymphoproliferative Disease of Childhood

Most patients present with acute onset of fever and general malaise after which patients develop hepatosplenomegaly and liver failure with or without lymphadenopathy. The disease has a rapid progression to multiple organ failure, sepsis, hemophagocytic syndrome, and death. Chronic EBV infection has been documented in some patients prior to the development of disease. Most cases secondary to acute primary EBV infection are $CD8^+$ whereas those in the setting of severe chronic active EBV infection (CAEBV) are $CD4^+$. EBER-1 is positive in the neoplastic T cells. The neoplastic cells exhibit clonal TCR gene rearrangement and harbor EBV in a clonal episomal form. All cases carry type A EBV, either with wild-type or the 30 base pair deleted product of *LMP1* gene. This is a life-threatening illness of children and young adults characterized by a clonal proliferation of EBV-infected T cells with an activated cytotoxic phenotype. It usually occurs shortly after primary acute EBV infection in previously healthy patients or in the setting of CAEBV. It has a rapid progression with multiple organ failure, sepsis, and death, usually from days to weeks. The most frequent sites of involvements are liver and spleen followed by lymph nodes, bone marrow, skin, and lung. The most typical phenotype of the tumor cells is $CD2^+CD3^+CD56^-$ and positive for cytotoxic proteins. Most cases secondary to acute primary EBV infection are $CD8^+$, whereas cases in the setting of severe CAEBV are $CD4^+$. EBV is always positive. The tumor cells have monoclonally rearranged TCR genes.

Hydroa Vacciniforme-Like Lymphoma

This is an EBV-positive cutaneous T-cell lymphoma occurring in children and associated with sun sensitivity. This condition affects primarily sun-exposed skin, in particular the face. The lesions present as papulovesicular eruptions that precede ulcerations and scarring. The clinical course is variable and some may have recurrent skin lesions. Late in the disease course, there is development of systemic symptoms such as fever, wasting, lymphadenopathy, and hepatosplenomegaly. The neoplastic cells exhibit clonal TCR gene rearrangement and harbor EBV in a clonal episomal form. It is still not clear whether severe mosquito-bite allergy, which is of NK derivation and EBV-associated, is part of Hydroa vacciniforme-like lymphoma or a distinctive entity within the spectrum of EBV-associated disorders. Both disorders are considered part of the spectrum of severe CAEBV, with a broad spectrum of clinical aggressiveness.

Ultimately, despite its rare occurrence in children and adolescents, PTCL remains a diagnostic and therapeutic challenge for this age group. While there continues to be progress in the identification of specific disease entities, improvements in the outcomes with treatment strategies have been slow to improve. A large number of developmental therapeutic agents are continually being examined in adults, where the numbers of patients enable such investigations. However, with the paucity of pediatric cases of PTCL, there will have to be extrapolation of adult data to improve on the outcomes of cases with advanced stage disease. As we learn more about the biology of these diseases and the potential benefits of specific targeted agents, decisions in treatment strategies will become more enlightened. Until a tried and true therapeutic regimen is discovered, it seems that children with advanced stage and/or refractory/recurrent PTCL may benefit from induction therapy followed by an alloSCT with reduced-intensity conditioning regimens.

Summary

T-cell malignancies in children and adolescents represent a heterogeneous group of neoplasms that arise from precursor T lymphocytes and a variety of mature T subsets. Most T-cell malignancies exhibit aggressive clinical behavior.

T-ALL and T-LBL represent 15% of childhood ALL and one-third of childhood and adolescent NHL respectively. Although the molecular genetics of T-ALL has been well studied, relatively little is known regarding the molecular pathogenetic mechanism involved in T-LBLs. It has been widely accepted that T-ALL and T-LBL likely represent different clinical manifestations of the same disease. Recent molecular analyses of T-LBLs however provide some evidence that they may exhibit distinct molecular genetic aberrations. Furthermore, many clinical trials have considered these diseases as one entity. The prevalence of *NOTCH* activation in T-ALLs has generated significant interest in the use of GSIs as a therapeutic strategy in T-ALLs. The results of clinical trials which are currently underway would be of interest. Within the mature T-cell malignancies, the *ALK* positive ALCLs are the most prevalent. Logically, the molecular aberration that defines this group of T-cell malignancies has led to the generation of a panel of potential tyrosine kinase inhibitors. Small molecule inhibitors to the *ALK* tyrosine kinase are currently under clinical investigation for relapsed ALCLs. Clearly, the number of developmental therapeutic agents available for children and adolescents is significantly lower than that for adults, where the numbers of patients enable such investigations. However, with the paucity of pediatric cases of PTCL, there will have to be extrapolation of adult data to improve on the outcomes of cases with advanced stage disease. As we learn more about the biology of these diseases and the potential benefits of specific targeted agents, decisions in treatment strategies will become more enlightened. Until a tried and true therapeutic regimen is discovered, it seems that children with advanced stage and/or refractory/recurrent PTCL may benefit from induction therapy followed by an alloSCT with reduced-intensity conditioning regimens. With improved diagnostic criteria for subclassification of T-cell neoplasms and better understanding of the molecular pathogenetic mechanisms, there is increasing optimism for greater availability of therapeutic agents for T-cell malignancies in children and adolescents.

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