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T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma: therapy in adults



A B S T R A C T

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) are aggressive neoplasms derived from malignant transformation of lymphoblasts committed to T-cell lineage. Because of their morphological, immunophenotypic and clinical similarities, they have often been thought to represent a spectrum of a single disease, and the distinction between them had sometimes been arbitrary. Following the pediatric experience, the main current therapies for both T-ALL and T-LBL in adults are based on intensive induction chemotherapy, including central nervous system prophylaxis, and a prolonged maintenance phase. Despite complete remission rates up to 80-90%, similar to those obtained in children, the prognosis in adults is less favourable, mainly because of high rates of relapse. A convincing prognostic model to determine which patients have to be offered more intensive consolidation, such as stem cell transplantation, is lacking. However, recent biological studies provided the evidence for a number of differences in the molecular and genetic profiles between T-ALL with different outcome and between T-ALL versus T-LBL. The precise definition of the aberrant molecular pathways relevant for the pathogenesis of neoplastic cells as well as the possibility to accurately evaluate the treatment response by minimal residual disease studies will probably be worthwhile in defining more precise prognostic models and in developing new target therapies.

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) derive from malignant transformation of T-cell precursors at various levels of differentiation. They are quite rare diseases in adults, accounting for 20-25% of acute lymphoblastic leukemia (ALL) and 1-2% of all non-hodgkin lymphomas (NHL) respectively.

Although originally recognised and treated as separate entities, it was subsequently accepted that T-ALL and T-LBL represent different manifestations of the same underlying disease because of

their morphological, immunophenotypic and genetic similarities. However, differences in the clinical and biological behavior and distinct gene expression profile have been observed.^{1,2}

They are aggressive diseases, with an increased incidence in adolescents and young adults and male predominance. T-ALL patients have an extensive bone marrow infiltration and involvement of extranodal sites, in particular the mediastinum, is common. Traditionally, T-LBL is defined by the absence of, or minimal (<25%) bone marrow involvement, and the

primary site of disease is the anterior mediastinum in the majority of cases. Localization at central nervous system (CNS), at diagnosis or during the course of disease, is frequent in both conditions.

Due to these similarities, recent WHO classifications^{3,4} summarize T-ALL and T-LBL in the same category of T-precursor lymphoblastic leukemia/lymphoma.

Treatment of T-cell acute lymphoblastic leukemia

The largest clinical reports on adult ALL treatment comprehend both B- and T-lineage cases, and only a few studies focus on T-ALL alone.⁵⁻⁷ Pediatric studies usually report a less favourable outcome for patients with T-lineage ALL.^{8,9} In adults the relationship between T-cell phenotype and outcome is more controversial (Table 1). While there is a general consensus about the irrelevance of immunophenotype for complete remission (CR) achievement following intensive induction chemotherapy, differences in long-term outcome between B-

and T-lineage ALL are seen in the majority of studies. Some reports correlate T-cell phenotype with a poorer prognosis,^{11,15} but several other studies suggest an improved outcome for these patients.^{10,13}

The international prospective trial MRC UKALL XII/ECOG 2993 enrolled more than 1,500 patients, thus representing one of the largest studies on adult ALL: at multivariate analysis the only risk factors predictive for better overall survival (OS) and disease-free survival (DFS) were age (less than 35 y), white blood cell count (less than 30×10^9 in B-lineage and less than 100×10^9 in T-lineage) and T-cell phenotype.¹⁶

Although some differences exist between treatment strategies in the various trials, the backbone of ALL induction treatments is similar, and CR rates of 80% or more are commonly achieved. Despite these good results, not far from those obtained in children, prognosis of adult T-ALL is much less favourable, mainly because of the high relapse rate.

Intensification of post-induction therapy is now a common feature in the majority of protocols, although there are no randomized stud-

Table 1. Prognostic value of immunophenotype in adult acute lymphoblastic leukemia clinical trials.

Study	Frequency		Complete remission			DFS		p
	B-ALL	T-ALL	B-ALL	T-ALL	p	B-ALL	T-ALL	
Boucheix <i>et al.</i> 1994 ¹⁰	361/562 (63%)	150/562 (26%)	74%	81%	ns	30.9% 3y	48.2%	0.005
Hallbook <i>et al.</i> 2002 ¹¹	131/153 (86%)	18/153 (12%)	-	-	-	38% 3y	25%	0.008
Takeuchi <i>et al.</i> 2002 ¹²	182/263 (69%)	29/263 (11%)	77%	79%	ns	31.2% 6y	47.2%	ns
Hoelzer <i>et al.</i> 1988 ¹³	115/248 (46%)	50/248 (20.1%)	71%	82%	ns	34% 5y	55%	0.01
Czuczman <i>et al.</i> 1999 ¹⁴	206/259 (79%)	44/259 (17%)	-	-	-	39% 3y	62%	0.01
Annino <i>et al.</i> 2002 ¹⁵	411/706 (58.2%)	134/706 (19%)	83%	85%	ns	34% 8y	27%	0.005

ies evaluating the most efficacious drug or drug combination in adults. For example, the observation that T-cell lineage blasts form fewer methotrexate (MTX) polyglutamates than those of B-cell blasts led to the intensification of MTX therapy in childhood T-ALL patients, obtaining a substantial improvement in the response.^{17,18} It is likely, however, that systematic administration of very-high doses of MTX to adult patients could determine an increased risk of treatment-related toxicity.

The role of allogeneic stem cell transplantation (SCT) as consolidation treatment for ALL patients in first CR has been investigated by various trials, but no studies specifically addressed the role of allogeneic SCT in the T-lineage subgroup of patients. A large randomized trial of allogeneic SCT (donor vs no donor) in adult Philadelphia-negative ALL recently demonstrated an improved 5-year OS of 53% vs. 43% ($p=0.01$) in patients with a donor and a significantly lower relapse rate ($p<0.001$).¹⁹ The benefit appears more evident for standard-risk patients, since high-risk patients are usually older and have a greater risk of non-relapse mortality

Maintenance therapy remains mandatory in those patients without a sibling or unrelated donor. The same UKALL XII/ECOG 2003 trial randomized patients without a matched donor between high-dose therapy with subsequent autologous SCT and conventional-dose maintenance chemotherapy. The analysis of 456 randomized patients showed that patients assigned to prolonged maintenance had better 5-year OS and EFS than those randomized to autologous SCT (46% and 41% vs. 37% and 32%, respectively, $p=0.03$).¹⁹ These results confirm the general evidence that autologous SCT has a limited role, if any, in ALL treatment. Relapsed T-ALL patients have a very poor outcome, and in many cases salvage treatments are ineffective. Recently, the nucleoside analog nelarabine has received FDA

approval for patients with refractory or relapsed T-cell ALL²⁰ and a number of other drugs are under evaluation in phase I and II trials.

Treatment of T-cell lymphoblastic lymphoma

The early studies in adult LBL using standard protocols for NHL, such as CHOP, COMP or mBACOD, obtained relatively low rates of CR (53-71%) and of DFS (30-53%).^{21,22} Improved results were subsequently reported with the use of more intensive chemotherapeutic approaches, originally designed for aggressive NHL, such as the Stanford/NCOG protocol²³ and the LSA2-L2 or LNH-84 regimen.²⁴ ALL-like regimens determined a substantial improvement of LBL outcome, and in multiple series CR rates of 72-100% and DFS of 62-67% have been reported.^{25,26} All these studies showed the optimal tolerability of such intensive regimens, with a particularly low rate of toxic deaths, probably due to the almost intactness of bone marrow reserve in LBL patients without significant bone marrow involvement.

Despite the lack of prospective randomized comparisons, it appears clear that the intensity and the duration of chemotherapy are correlated with the outcome in LBL, and that ALL-like regimens are better than NHL-like regimens. Nevertheless, adult patients show a higher relapse rate as compared to childhood LBL patients, even when similar regimens are employed. In the multicenter German study involving quite a large series of 45 T-LBL adults patients²⁶ the CR rate after intensive chemotherapy was 93%, but 36% of patients relapsed within 1 year, the majority of relapses (7 of 15) being confined to the mediastinum, despite prophylactical mediastinal irradiation (24 Gy). Another major cause of failure in adults is CNS disease: the reported

CNS relapse rate ranges from 3-42% in studies using intrathecal chemotherapy prophylaxis alone, and from 3-15% in studies using a combination of cranial irradiation and intrathecal chemotherapy.²⁷

The effective role of both mediastinal and cranial irradiation in adults has been debated, since the German experience of BFM group in childhood LBL treatment showed that higher doses of chemotherapy are as effective as irradiation in preventing relapse, thus avoiding the long-term toxicity of radiation therapy.²⁸ It is not clear, however, whether such intensive chemotherapy regimens would be well tolerated in adults.

In order to improve the outcome of adult LBL patients, various chemotherapy programs that integrate consolidation with either autologous or allogeneic SCT have been proposed. Levine et al reported a large series of 204 LBL patients who underwent autologous (n=128) or HLA-identical sibling (n=76) SCT.²⁹ Patients who received allogeneic SCT had a higher transplant-related mortality (TRM) than autologous transplant recipients. Early relapse rates after autologous or allogeneic SCT were similar, but significantly lower relapse rates were observed in allogeneic SCT recipients, at 1 and 5 years, possibly due to a graft vs leukemia effect. In this experience, however, benefits of a better disease control were counterbalanced by a very high TRM, so that 5-year survival was not different between allogeneic or autologous SCT recipients.

The role of autologous SCT as consolidation treatment is controversial: in a prospective randomized study on 65 adult LBL patients, the use of autologous SCT in first remission produced a trend for improved relapse-free survival but did not improve OS as compared to conventional-dose consolidation and maintenance treatment.²⁴

Future directions: risk-adapted/molecular-target therapy

Despite the recent improvement in treatment approaches, the prognosis of T-ALL/T-LBL remains still unsatisfactory in many patients. Although current ALL treatments are able to determine a haematological CR rate of 80% or more, molecular CR usually do not reach 60%, thus explaining the high rate of relapse in adult ALL.³⁰

So far studies that attempt to identify prognostically distinct subgroups among T-ALL/T-LBL patients are scanty.^{5,7,31} A study from the Italian cooperative group GIMEMA showed that in T-ALL the level of maturation of blasts (pro-T + pre-T vs. cortical-T + mature-T), as well as the expression of myeloid antigens (CD13 and CD33) or CD34, and multidrug-resistance (MDR1) protein expression and function have a significant impact on CR achievement and survival.⁷

The explanation of this heterogeneous behavior is that the T-ALL/T-LBL is not a single disease, but rather a group of biologically distinct diseases that target the same cells of origin, the T-cell precursors.³²⁻³⁴

Moreover the response to chemotherapy is influenced by the interactions between several factors. Some of these variables are characteristics of leukemic cells, such as the expression of genes that regulate their susceptibility to treatments and their propensity to undergo apoptosis. However, also variables related to the host, such as age or polymorphisms in genes that metabolize drugs, or pharmacological variables, such as drug pharmacodynamics and drug interactions, influence treatment response. Therefore, a deeper knowledge of the molecular features of neoplastic cells is essential for precise T-ALL/T-LBL prognostication and monitoring in a risk-adapted program of therapy, and can provide useful clues for the new targeted therapies.³⁵

Over the last 20 years, much progress has been made in the discovery of molecular abnormalities and in the explanation of pathogenesis of T-precursors Leukemia/Lymphoma. By using conventional cytogenetic studies only 25-50% of T-ALL/T-LBL cases showed abnormal karyotype. The introduction of new tools for molecular-genetic analysis, such as fluorescent in situ hybridization (FISH), mutation analysis by gene sequencing and dHPLC, gene expression profiling and comparative genomic hybridization (CGH) analysis, increased the number of cases of T-ALL/T-LBL with recognised molecular-genetic abnormalities.^{34,36}

These genetic defects include chromosomal translocations, deletions, amplifications, and point mutations. Many of genes involved normally play important roles in T-cell ontogenesis by controlling proliferation, commitment and differentiation of T-cells. In a multi-step pathogenesis vision, the differential combinations of a number of these defects cause the developmental arrest of normal thymocytes at particular stage and delineate distinct T-ALL/T-LBL subgroups with precise clinical and prognostic features.³²⁻³⁴

The known abnormalities can be grouped in different ways. Generally, there are two types of mutations: those that may determine the molecular specific subtype of T-ALL/T-LBL and those that synergize with the first type during pathogenesis by affecting genes that normally play a role in cell-cycle regulation, self-renewal and T-cell commitment, (pre)TCR signaling, T-cell differentiation or by leading to aberrant tyrosine-kinase activation.³³

The first type of defect mainly affects thymocytes development by promoting the differentiation arrest at specific stages in T-cell ontogenesis. This group comprises mutations that interfere with the functions of basic helix-loop-helix proteins (TAL1/2, LMO1/2,

LYL1), mutations that cause abnormal expression of homeobox genes (HOXA genes, TLX1, TLX3), and mutations that activate the oncogene MYB.^{33,34}

On the other hand, the second type of mutation influences basic cellular functions. For example, the cell cycle may be affected as result of deletion/inactivation of the CDKN2A/2B genes that encode for p16 and p15 respectively, and act as inhibitors of the complex cyclin-D/cyclin-dependent kinase 4, or by over expression of the gene that encodes for cyclin D2 (CCND2 gene).³³ Self-renewal is frequently influenced by activation of the NOTCH1 pathway by mutations that directly target NOTCH1 or that inactivate FBXW7 which controls the degradation of protein like NOTCH1.³²⁻³⁴ Finally mutations of genes that regulate the signaling of TCR (LCK, RAS) or that encode for tyrosine-kinases (ABL1, JAK2, FLT3) may be identified.^{33,34}

Many of these molecular abnormalities, alone or in combination, have been associated with distinct clinical features, such as the immunophenotypic characteristics of leukemic cells or the T-ALL vs. T-LBL presentation. Moreover they identify different prognostic entities which have so far been under-considered.^{33,34}

Unfortunately, to date, and in contrast to B-precursor leukemias/lymphomas subgroups, the molecular-genetic anomalies in T-ALL and in T-LBL are not used for clinical-therapeutic stratification. However the routine investigation of genetic defects in T-precursor neoplasms will be crucial to further improvement of treatment outcome especially by targeting specific molecular defects (Table 2).

Up to now there are no clinically usable drugs for specific molecular targeting in the T-ALL/T-LBL patients with the possible exception of T-ALL cases with fusions of the ABL1 gene (NUP214-ABL1, EML1-ABL1 or ETV6-ABL1), in which the ABL kinase

Table 2. Genetic defects and potential targets of therapies in T-precursor neoplasms.

<i>Genetic defect</i>	<i>Frequency (%)</i>	<i>Target</i>	<i>Potential therapy</i>
CDKN2A/B inactivation	Unknown	Hypermethylation	DNA methyltransferase inhibitor
SIL-TAL1	10	TAL overexpression	HDAC inhibitor
TAL1 translocation	3		
CALM-AF10	10	hDOT1L	Histone H3K79 methyltransferase inhibitor
MLL-ENL			
MLL-AF10			
SET-NUP214			
NUP214-ABL1	<6	ABL1 activation	ABL kinase inhibitor
EML1-ABL1	<1		
ETV6-ABL1	<1		
BCR-ABL1	<1		
LCK translocation	<1		
RAS mutations	Unknown	RAS activation	Farnesyltransferase inhibitor
ETV6-JAK2	Unknown	JAK2 activation	JAK2 inhibitor
NOTCH1 mutation	>60	NOTCH1 activation	Gamma-secretase inhibitors
FBXW7 mutations	>20		
PTEN mutations	Unknown	PTEN inactivation	PI3K/AKT inhibitors
PTEN deletions		AKT activation	

inhibitors may be available.³⁷ Therefore, until molecular target therapies become available, the more suitable option for T-ALL/T-LBL treatment is a risk-adapted therapy based on molecular measurement of treatment response.

The leukemia-associated molecular features useful for minimal residual disease (MRD) identification include clonally rearranged TCR genes, chromosomal abnormalities and fusion transcripts amplifiable by polymerase chain reaction (PCR) as well as abnormalities in protein expression detectable by flow cytometry. Because MRD assessment is considerably more powerful than traditional morphologic monitoring, it is being incorporated to guide therapy into many protocols in childhood ALL.³⁵

Indeed, in recent years, many studies have demonstrated the clinical relevance of MRD levels during the early phases of treatment of ALL also in adults. Early clearance of MRD

indicates a high chemosensitivity of the leukemic clone and is associated with excellent overall outcome.^{30,38-42}

Although T-LBL are usually characterized by localized disease, they may also take advantage of this approach due to the not unfrequent presence of minimal bone marrow involvement at presentation detectable by highly sensitive methods, such as flow cytometry and real-time quantitative PCR.⁴³

In addition to measuring early response to treatment and to guiding the intensification or possibly the deintensification of treatment, MRD studies have several other applications in the clinical management of T-ALL/T-LBL patients. For example, they can detect an early relapse in order to optimize the timing of rescue therapy, such as hematopoietic stem cell transplantation (HSCT). After HSCT, MRD assessment can be used to modulate the immunosuppression or to guide the adminis-

tration of donor lymphocyte infusions. Finally, MRD assays can also provide a powerful tool to quickly assess the effectiveness of new target therapy.³⁵

Conclusions

In summary, despite the rarity of the diseases and the large number of approaches applied in the treatment of adult T-ALL and T-LBL, some general considerations can be made: a) due to the similar biological features, T-ALL and T-LBL should be treated with intensive chemotherapy induction schemes, including CNS prophylaxis; b) a prolonged maintenance therapy is required to reduce the risk of relapse in both diseases; c) an intensive consolidation, based on allogeneic SCT, should be offered to young high-risk patients.

However, due to the lack of a reliable prognostic model based on conventional parameters (such as age, sex, stage IV disease, extranodal or CNS involvement, elevated levels of LDH), the precise definition of prognostic subgroups will be based on the information about the molecular profile of neoplastic cells as well as on the possibility to accurately evaluate the treatment response by MRD studies.

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