T-CELL ACUTE LYMPHOBLASTIC LEUKEMIA AND LYMPHOBLASTIC LYMPHOMA

Josep-María Ribera

Clinical Hematology Department . ICO-Hospital Germans Trias i Pujol. Badalona. Josep Carreras Leukemia Research Institute. Universidad Autònoma of Barcelona, Spain

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LL) are neoplasias of immature T-cell precursors considered as a unique biological entity in the 2008 World Health Organization Classification of Hematologic Neoplasias[1]. Both entities are arbitrarily separated by a cut-off point of 20%-25% of blast cells in the bone marrow. There is a general agreement that T-ALL and T-LL are different forms of the same entity, being T-LL a localized disease and T-ALL a systemic disease. In adults T-LL is an infrequent type of non-Hodgkin's lymphoma (NHL), representing about 2% of cases and having a bimodal incidence, with higher frequencies in patients less than 20 years and in those aged more than 50 years. In children T-LL represents about 30% of NHL. On the contrary, T-ALL accounts for 25% of ALL in adults and 12-15% in children and the highest peak of incidence occurs in adolescents and young adults.

However, the results of genetic profiling have shown differences between T-LL and T-LL[2]. In addition, immunophenotypic studies in T-ALL show cortical and mature subtypes in most of the cases, with a probable relationship with the higher frequency (more than 90%) of mediastinal involvement. On the contrary T-ALL show cortical phenotype in 50% of cases, pre-T in 25% and mature T in the remaining 25%, with a frequency of mediastinal involvement of 60%-70%. From a clinical point of view, both entities have a male predominance and show a similar frequency of CNS involvement (5%-10%) at diagnosis[3] (Table 1).

TREATMENT OF T-CELL LYMPHOBLASTIC LYMPHOMA

Treatment of T-LL has evolved over time from conventional high-grade NHL schedules to ALL-derived protocols.

Schedules for aggressive lymphomas

CHOP-like regimens have provided low complete remission (CR) (50% -70%) and disease-free survival (DFS) (20%-50%) rates (Table 2). Modified CHOP regimens adding asparaginase, CNS pro-

Table 1. Main clinical and biologic characteristics of T-cell acute lymphoblastic leukemia (T-ALL) and lymphoblastic lymphoma (T-LL)

Characteristic	T-ALL	T-LL
Male gender	70%-75%	65%-75%
Median age, yr.	30	25
Mediastinal mass	60%-70%	90%-95%
Pleural effusion	<5%	35%-45%
CNS involvement at diagnosis	5%-10%	<10%
Raised serum LDH	80%	70%
Bone marrow infiltration	100%	20%-25%
Phenotype		
Pro-T/pre-T	25%	10%
Cortical	50%	80%
Mature	25%	20%
NOTCH mutations	30%-60%	30%-60%
FBXW7 mutations	15%-25%	15%-25%
Oncogenes		
TAL1	20%	0%
TLX1	5%	0%
TLX3	20%-25%	0%
SIL/TAL	20%	0%

phylaxis and maintenance treatment improved the CR rate (80% -100%), but the impact on DFS was low. More intensive regimens (LSA2-L2, LNH-84) only provided modest improvement in survival, at least in adults. Inclusion of hematopoietic stem cell transplantation (HSCT) was associated with better DFS and overall survival (OS) in some studies.[3]

Chemotherapy regimens for ALL

The first trials including an ALL-based therapy (L2, L10 y L17) showed CR rates ranging from 55% to 100% and DFS rates ranging from 45% to 70%. Probably, the seminal study was conducted by the German Group BFM, showing an event-free survival (EFS) rate of 90% in children with T-LL using a protocol for ALL[4]. In adults the CR duration was 65%.[5] Other regimens such as Hyper-CVAD have also shown CR rates over 90%, with DFS of 60%-70%[6]. These and other regimens include high-dose methotrexate (HD-MTX), cytarabine (HD-AC) and asparaginase as essential drugs (Table 2). Recent pediatric trials have shown DFS probabilities of 80%-85%.

CNS prophylaxis has dramatically reduced CNS relapses. Combined intrathecal and high-dose intravenous therapy has allowed omitting cranial irradiation in both children[7] and adults[6], although cranial radiotherapy is still administered by some groups[5].

Most of the relapses occur in the mediastinum, in spite of prophylactic mediastinal irradiation performed by some groups at the end of therapy. However, ALL-type therapies with HD-MTX have allowed omitting mediastinal irradiation, at least in children, thus avoiding long-term squeals [4]. However tolerability of very HD-MTX is poor in adults and consequently mediastinal irradiation is still of current practice. Probably modern imaging techniques such as PET scan will be of great value for the selection of candidate patients to receive mediastinal irradiation. Given the lack of consistent prognostic factors in T-LL is probable that these imaging techniques, together with the study of minimal residual disease (MRD) (see below) will help to select alternative treatments such as new drugs or HSCT.

Hematopoietic stem cell transplantation

Autologous HSCT or, less frequently, allogeneic HSCT have been used as consolidation therapy in patients with T-LL with high-risk features. In some studies a trend for a better relapse-free survival has been observed in transplanted patients in first CR, but this has not been translated into improvement in OS on comparison with chemotherapy[8]. Retrospective studies from HSCT registries have shown that the higher transplant-related mortality (TRM) observed in allogeneic HSCT (20% vs. 3% in autologous HSCT) was counterbalanced by a low relapse rate (35% vs. 55%), resulting in a similar OS probability (40%)[9], not different from that observed with chemotherapy alone. Prospective studies using autologous HSCT specifically designed to avoid the selection bias observed in the registry studies have provided similar results on comparison of autologous HSCT vs. chemotherapy by intention-to-treat. On the other hand there is not a prognostic model for an adequate identification of high-risk T-LL patients, making difficult the selection of candidate patients to HSCT in first CR. Beyond first CR autologous HSCT shows DFS rates of 35%-50% wheareas allogeneic HSCT provides survival rates of 14%-46% according to the different studies.[9]

Treatment of relapsed or refractory disease

Salvage chemotherapy followed by HSCT provides DFS rates of 40% for relapsed patients but only of 15% for those with refractory disease. Late relapses in patients submitted to autologous HSCT can be rescued with allogeneic HSCT. However,

Table 2. Overall results of treatment of lymphoblastic lymphoma in adults according to the type of therapeutic schedule

Therapeutic schedule	Number of studies	Number of patients	Median age, yr.	CR (%) (range)	DFS (%) (range)
NHL, conventional	5	114	28-45	58 (53-17)	36 (23-53)
NHL, modified	5	112	14-22	92 (79-100)	49 (23-56)
NHL aggressive	4	64	25-34	67 (57-84)	51 (35-75)
ALL type	9	282	22-37	80 (55-100)	56 (45-67)

refractory patients or those with early relapses should be included in clinical trials with new drugs (new purine analogues, monoclonal antibodies, proteasome inhibitors, m-TOR inhibitors, or gamma secretase inhibitors, among others)[3].

TREATMENT OF T-ALL

T-ALL is a highly heterogeneous disease from the genetic point of view[10]. Deletions, mutations, duplications and other genetic rearrangements have prognostic significance and some of them could have therapeutic implications (Table 3).

Results of T-ALL therapy in children

Traditionally the prognosis of T-ALL was poor than that of precursor B-ALL, at least in the poor risk group. However, with the use of current intensive therapies, the results have markedly improved and are in fact similar to those obtained in B precursor ALL (CR rates of 95%-100% and DFS 80%-85%). This improvement has been attributed to the use of HD-MTX (5 g/m^2)[4,11], PEG-asparaginase[12] and dexamethasone. In a recent randomized study administration of four doses of MTX (5 g/m^2) has shown favorable results in T-ALL but not in T-LL[11]. In modern protocols CNS irradiation has been omitted as CNS prophylaxis. Current studies are evaluating the addition of nelarabine to front line therapy and several clinical trials are incorporating new drugs in genetically defined subsets of T-ALL (Table 3).

The main prognostic factors are poor prednisone response on day 8, MRD higher than 10^{-3} at the end of induction and/or consolidation and several molecular rearrangements [13]. In this sense *NOTCH* activation is associated with good early response, but only is some studies has a favorable impact on survival[14]. On the other hand pro-T ALL is associated with poor prognosis, with EFS of only 30% despite the use of allogeneic HSCT. Recent studies are evaluating the usefulness of high-dose dexamethasone in these patients.

Recent results have demonstrated that late relapses (beyond 2.5 yr. from diagnosis) are in fact a new T-ALL in one third of cases[15].

Results of T-ALL therapy in adults

The results of T-ALL in adults are clearly poorer than those obtained in children, with CR rates around 90% and DFS of 40%-45%[16]. The UKALL XII/ECOG 2993 study showed a CR rate of 94% and 5-yr OS of 48% in 356 adults[17] and similar results have been published by other groups[16]. Recently, with the use of pediatric-inspired protocols including asparaginase and HD-MTX, the DFS has raised to 60%. The main prognostic factors are age higher than 55 yr., WBC count over 100x10^9/L, slow

Table 3. Molecular characteristics, frequency, prognosis and results of therapy in T-ALL in children

Subtype	Frequency (%)	Clinical significance	EFS 5yr (%)
TAL/LMO	15–30	Good prognosis in some studies. Possible response to histone deacethylase inhibitors (HDACI)	?
HOX11	7-8	Good prognosis	?
HOX11L2 (TLX3)	20-24	Poor prognosis in some studies	?
HOXA	4-5	Poor prognosis. Possible response to the HDACI 3K79	?
NUP214-ABL1	5	Sensitivity to thyrosine kinase inhibitors	50
MLL-ENL	2-3	Good prognosis	80-90
Pro-T/Pre-T	12	Poor prognosis Myeloid or stem cell markers	30-35
NOTCH/FBXW7	50	Favorable prognosis Possible response to NOTCH inhibitors	90
PTEN-P13K-AKT pathway	50	Poor prognosis?	?
CDKN2A/2B	70	Possible response to DNA methyltransferase inhibitors	¿?

response to therapy, high MRD level after induction or consolidation, several phenotypic (co-expression of CD13, CD33 and/or CD34 y, especially, pro-T or mature T phenotypes) and molecular features (absence of *NOTCH1/FBXW7* or *HOXA/TLX1* rearrangements, expression of *IGFBP7*, *HOX11L2* rearrangement, high expression of *ERG* and *BAALC*, *SIL-TAL* rearrangement, among others)[18,19]. Many of these molecular abnormalities are correlated with the stage of T-cell development.

Hematopoietic stem cell transplantation

The excellent results obtained in children with T-ALL have dramatically restricted the indication of allogeneic HSCT in first CR to a minority of high-risk patients. Allogeneic HSCT is the treatment of choice in children in second CR following an early relapse.

The situation in adults is different due to the poorer results obtained with chemotherapy. Allogeneic HSCT is indicated in high-risk patients in first CR, whereas the need of HSCT in standard-risk patients is questionnable[20]. Allogeneic HSCT should be performed in all patients beyond first CR.

Minimal residual disease

In children with B-precursor ALL MRD is one of the most powerful prognostic factors and is a key element for therapeutic decisions in modern protocols. MRD measurement is also useful in T-ALL, especially at the end of induction and/or consolidation[21,22] and constitutes a decision tool for treatment intensification (i.e.: HSCT) in patients with poor molecular response.

In T-LL MRD is less standardized. However, some immunophenotypic studies in pediatric T-LL have demonstrated tumor cells in peripheral blood (i.e.: with expression of CD3 and TdT) in two thirds of patients, and most important, their amount and pattern of clearance were correlated with the relapse probability.[23]

New drugs in T-ALL

Several drugs have demonstrated their usefulness in patients with relapsed or refractory T-ALL. The most relevant are nelarabine and clofarabine, which are currently investigated in earlier phases of the disease. Other drugs include new antifolates, new nucleoside analogues (forodesine), monoclonal antibodies (alemtuzumab), thyrosine kinase inhibitors (in patients with *NUP214-ABL1* rearrangement), gamma-secretase inhibitors (in combination with corticosteroids in patients with *NOTCH-1* rearrangement), farnesil transferase inhibitors and demethylating drugs, among others.

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