T CELL LYMPHOMA/LEUKEMIA: CURRENT TREATMENT APPROACH

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Introduction

T-cell acute lymphoblastic leukemia (T-ALL) and T-cell lymphoblastic lymphoma (T-LBL) are immature T-cell malignancies considered as a biologic unit in the World Health Organization Classification, termed precursor lymphoma/leukemia. Both entities are arbitrarily separated by a cut point of 25% bone marrow (BM) infiltration. It is generally accepted that T-LBL and T-ALL represent different manifestations of the same disease, being T-LBL an early localized manifestation and T-ALL a large stage with a systemic spread.

In adults T-LBL is a rare form of non-Hodgkin's lymphoma (NHL), with an incidence less than 2% and a bimodal age distribution, with higher rates in individuals younger than 20 and in those older than 50 years. The incidence is higher in children, where T-LBL constitutes about 30% of NHL. In contrast T-ALL constitutes about 25% of ALL in adults and 12-15% of ALL in children.

However, some dissimilarity is observed between these two entities. Gene expression profiling data have shown differences between these two entities. In addition, although immunophenotypes of T-LBL and T-ALL are identical, they differ in frequency, with a higher rate of cortical and mature immunophenotypes in T-LBL, which is probably related to the higher rate (>90%) of mediastinal tumors.

From the clinical point of view, both entities show a younger age, male predominance and a similar incidence of initial central nervous system (CNS) involvement.

Treatment approaches in T-LBL

Therapeutic approaches for T-LBL have changed over time, moving from conventional protocols for high-grade NHL to protocols for T-ALL.

Chemotherapy regimens designed for NHL

CHOP-based regimens yielded low complete remission (CR) rates (50%-70%) and rates for disease-free survival (DFS; 20%-50%). A modified CHOP regimen with additional application of asparaginase, CNS prophylaxis and maintenance therapy, CR rates improved (80%-100%), but the impact in DFS was minimal. More intensive NHL regimens (LSA2-L2 or LNH-84) only showed modest improvements in survival. The inclusion of stem cell transplantation (SCT) in these regimens yielded a more favorable DFS (75%) and overall survival (OS; 85%)

Chemotherapy regimens designed for acute lymphoblastic leukemia

Earlier studies with different ALL-type regimens (eg, L2, L10, L17) showed CR rates between 55% and 100% and DFS ranging from 45% to 70%. Other regimens such as hyper-CVAD have shown CR rates over 90% and DFS of 70%. Other groups such as the German Multicenter Study for Adult ALL (GMALL) have shown similar results. The aggressive CNS prophylaxis has dramatically reduced the frequency of CNS relapses. Most of the relapses occur in the mediastinum, despite prophylactic mediastinal irradiation. In childhood T-LBL, the results of ALL-type regimens are superior, with CR of 90%-100% and OS rate higher than 85%.

Stem cell transplantation

Data from studies of SCT, either as autologous or –to a lesser extent- as allogeneic, have to be interpreted with caution because of the selection bias and the source of information (eg, registry-based). The results of large retrospective studies from large international SCT databases on autoSCT and

alloSCT not surprisingly showed higher transplant-related mortality (TRM) in alloSCT (about 20%) than in autoSCT (3%), being counterbalanced by a lower relapse rate in alloSCT (35% vs.55%), resulting in a similar survival (about 40%). The overall results of these retrospective studies were not superior to results with chemotherapy in ongoing trials. Prospective studies with autoSCT designed to prevent the selection bias of registry-based studies yielded similar results as chemotherapy in an intent-to-treat analysis. Therefore, clear indications for SCT in first CR are missing; it should therefore be restricted to relapsed patients.

Residual mediastinal tumors

The mediastinum is the most frequent site of relapse in T-LBL. In some studies the rate of reduction of mediastinal mass was correlated with relapse, and inferior outcome was observed in patients with residual mediastinal tumors after treatment. In pediatric T-LBL low mediastinal recurrence rates are achieved by intensive chemotherapy including rigorous early application of cyclophosphamide and ARA-C and, specially, high-dose methotrexate (HD-MTX). This approach has allowed avoiding mediastinal irradiation. This intensive chemotherapy approach is not feasible in adult patients. For them, the most frequent approach for prevention of mediastinal recurrence is mediastinal irradiation. It is possible that modern image techniques for detection of active mediastinal disease, such as PET-CT, will help us to select those patients candidate to mediastinal irradiation or even to treatment alternatives such as new drugs or SCT.

Treatment approaches in T-ALL

Chemotherapy regimens

The chemotherapy schedules in pediatric and adult T-ALL are in general identical to those used in B-precursor ALL, although the results are slightly inferior. Complete remission rates of 95%-100% are usually achieved in children an 85%-95% in adults. The use of increased doses of asparaginase and HD-MTX has resulted in survival rates over 80% in children and between 40% and 60% in adults. In modern protocols using intrathecal and HD systemic CNS-directed therapy (HD-MTX and HD-AraC) CNS irradiation has been omitted as CNS prophylaxis.

Stem cell transplantation

The excellent overall results in pediatric T-ALL have reduced the alloSCT indication in first CR to a minority of high-risk T-ALL patients. Thus, alloSCT is only performed in patients in second CR after early relapse. Autologous SCT is not indicated in any case.

The situation in adults is different, because the results of chemotherapy are poorer than in children. It is currently accepted that alloSCT is indicated in first CR in patients with high-risk features; eg, age over 35 yr, WBC count over $100x10^9$/L, late time of CR or poor clearance of minimal residual disease (MRD). For some groups (eg, GMALL) early-T or mature-T phenotypes are also considered as high-risk features. The indication of alloSCT for the remaining patients is questionable. In general it could be stated that those patients who profit with chemotherapy alone, eg, having survival of 50%-60% or more, should probably not be candidates for alloSCT until it has be shown that SCT results are superior to these chemotherapy results. There is no indication for autoSCT in T-ALL, although the value of autoSCT in those patients with low MRD level after consolidation therapy should be further investigated.

Minimal residual disease

In children with B-precursor ALL MRD is one of the most powerful prognostic factors, and is a key element for making treatment decisions in modern protocols. MRD measurement is also useful in T-ALL and is used to define molecular response (eg, MRD below 10^{-4}), to predict relapse (eg, the detection of molecular relapse –MRD above 10^{-4} in a patient with a previous molecular CR-) and also for treatment decisions (eg, for risk assignment or to perform alloSCT). MRD results must be standardized and integrated in specific protocols in order to make adequate treatment decisions.

In T-LBL there are so far no data to evaluate MRD, although recent reports in childhood T-LBL have detected circulating tumor cells by immunophenotypic study, whose level was correlated with the relapse probability.

New biologic prognostic factors

Molecular studies in T-ALL have shown that overexpression of HOX11, HOX11L2, SIL-TAL1 and CALMAF10 is associated with stage of maturation and prognosis. Some groups have observed inferior prognosis of high expression of the transcription factors ERG and/or BAALC, overexpression of HOX11L2 and SIL-TAL-positive ALL. On the contrary, low expression of ERG and BAALC as well as

overexpression of HOX11 is associated with favorable outcome. In addition, the frequent NOTCH1 activating mutations seem to have prognostic and therapeutic relevance. These new biologic prognostic factors might serve to identify pathogenetic mechanisms and therapeutic targets.

New drugs in T-ALL

In recent years the therapeutic armamentarium in ALL has substantially increased. As far as T-ALL concerns, there are new drugs approved for refractory or relapsed patients, including nelarabine and clofarabine, among others. These two drugs are currently investigated in early phases of the disease. Other drugs include new antifolates, new nucleoside analogues (eg, forodesine), or monoclonal antibodies such as alemtuzumab. Thyrosine kinase inhibitors such as imatinib are evaluated in the minority of T-ALL patients with *NUP214-ABL1* rearrangement, and gamma-secrease inhibitors together with steroids are actively investigated in cases with *NOTCH-1* rearrangement. Farnesil transferase inhibitors and demetylating agents could also be of interest.

These and other drugs will open the window for further improvements in the results of treatment of T-ALL and T-LBL patients.