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Pediatric T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma therapy

T-cell acute lymphoblastic leukemia and T-cell lymphoblastic lymphoma in childhood are recognized to be two different pathologies with different biological basis and are treated according to different pediatric protocols.

Acute lymphoblastic leukemia (ALL) is the most common type of cancer in children. Although it may affect children of any age, there is a peak modal distribution between 3 and 6 years.

Recent advances in the treatment of childhood ALL may be regarded as a paradigm of the effectiveness of medical science in the management of formerly incurable diseases. Optimal use of the same antileukemic agents that were developed from the 1950s through the 1980s, together with a stringent application of prognostic factors for risk-directed therapy in clinical trials, has resulted in a steady improvement in treatment outcome, so that the current cure rate has now risen to about 80%. Emerging results suggest that a cure rate of nearly 90 percent will be attained in the near future.[1,2] From 2000 to 2006, the AIEOP-BFM ALL Consortium performed the largest international trial (AIEOP-BFM ALL 2000) in which the stratification and treatment adaptation due to early molecular response to therapy was prospectively applied[3-4] as shown in Figure 1.

T-cell Acute Lymphoblastic Leukemia (T-ALL) is a clinically homogeneous pathologic entity with a high frequency of treatment failure. T-ALL accounts 15% of all newly diagnosed pediatric ALL cases, and is clinically regarded as a high-risk disease with a relapse rate of about 30%.[5] About a fifth of children with T-ALL succumb to the disease, suggesting an unrecognised biological heterogeneity that might contribute to drug resistance. The five-year event-free survival for childhood T-ALL reported in literature by AIEOP Study Group is 65.7%[6] but unpublished results suggest that a cure rate ranging 70-80% will be attained with future generation of protocols. Present protocols for intensive treatment of T-ALL yield results similar to those in patients with non–T-ALL. As recently postulated, T-ALL originating from early T-cell precursors (ETP), a defined subset of thymocytes that retain stem-cell-like features, would respond poorly to lymphoid-cell-directed therapy.[7-8] ETP-ALL is previously unrecognised distinct pathobiological entity that confers a poor prognosis if treated with standard intensive chemotherapy; its early recognition, by use of the gene expression and immunophenotypic criteria, is essential for the development of an effective

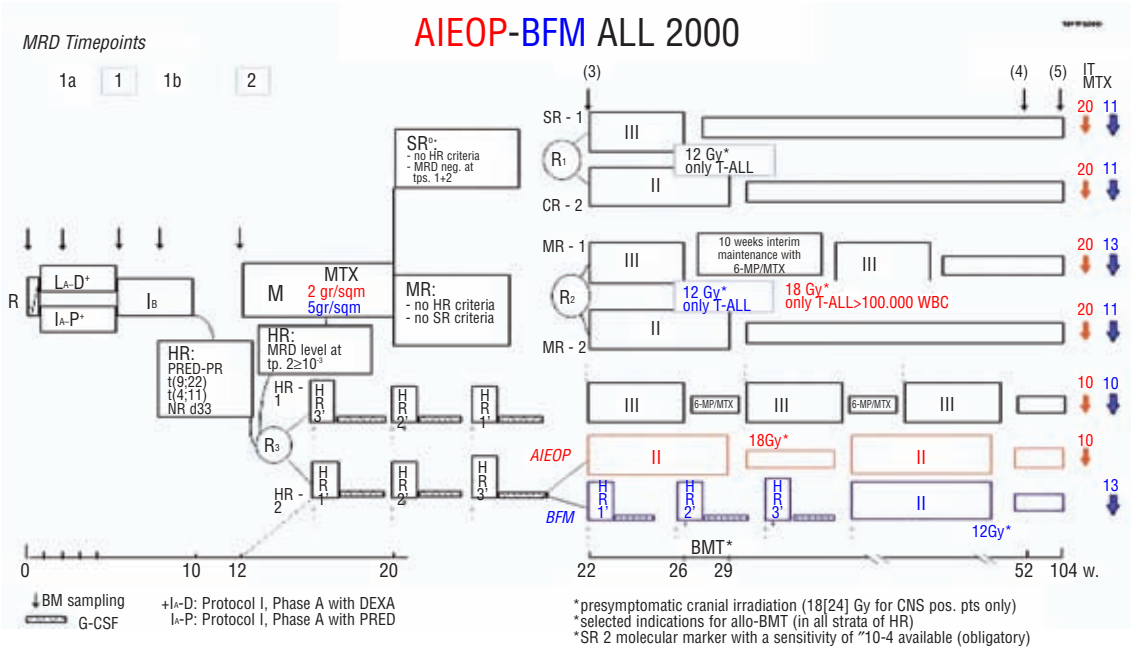

Figure 1.

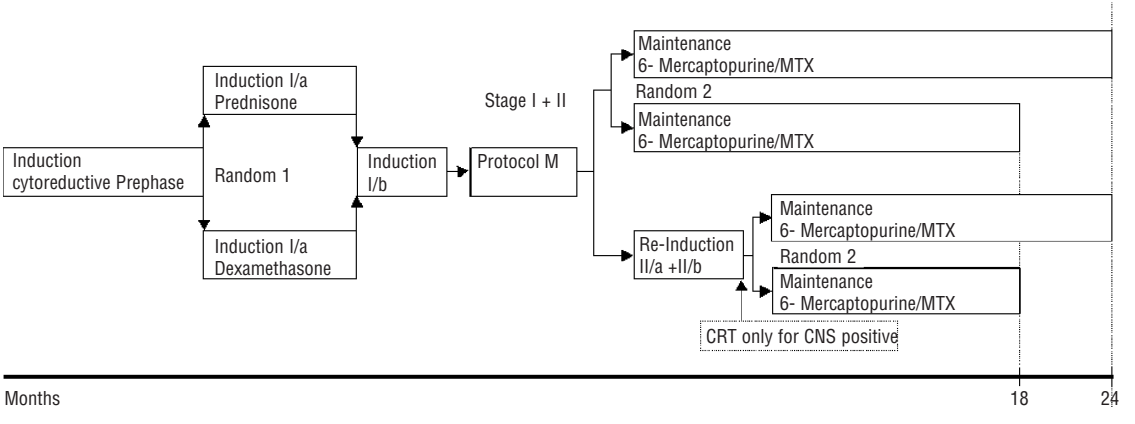

Figure 2. Treatment plan EURO-LB 02 fot T-cell lymphoblastic lymphoma.

clinical management strategy. Until recently the biological knowledge of T-ALL has been rather limited. The introduction of novel technologies has allowed to reveal an increasing number of alterations. The most relevant results have been obtained by using FISH, molecular biology and gene expression profiling, which have enabled five subgroups to be recognized; immature/*LYL1, TAL1, HOX11, HOX11L2* and *HOX*.2.[7] By now we know that deregulation of critical signalling pathways, in particular, NOTCH1, PI3K/Akt, MAPK, Jak/STAT and TGF-β, contribute to T-ALL.[9-10] NOTCH1 encodes a member of the transmem-

brane protein family which plays a role in the developmental processes of a variety of tissues. Constitutive NOTCH1 signalling in hematopoietic progenitors disrupts both normal T-cell and B-cell development and leads to T-cell cancers. The future of treatment for leukemia resides in defining the molecular pathways underlying the pathogenesis of this disease and in further elucidation of pharmacogenetic factors of the host. Extensive research has allowed a molecular profile of T-ALL to be defined. Some lesions have been well characterized, while others require further research. The identification of molecular lesions is leading to the generation of specific inhibitors, the clinical use of which may lead to a revision of the management of T-ALL patients.[11] At this moment the early response to treatment still represents the most important parameter to understand the clinical course of T-ALL. T-ALL patients with adequate response to the prednisone prephase (non-HR T-ALL) are expected to have a favourable outcome due to the initial use of dexamethasone.[12] In AIEOP-BFM ALL 2000 patients with T-ALL together with high-risk patients were the only ones which still received preventive cranial radiotherapy (pCRT). In AIEOP-BFM ALL 2008, non-HR T-ALL patients with initial WBC of <100 000/μL are no longer irradiated either in BFM or AIEOP. Allogenic Stem Cell Transplantation (SCT) could improve EFS of HR T-ALL and the indication for transplantation should be continuously evaluated in light of improvements in this procedure and in chemotherapy. Additional new chemotherapy agents including Nelarabine, a purine nucleoside analogue that is selectively activated in T cells and the purine nucleoside antimetabolite Clofarabine, approved for use in relapsed LAL, may be used in frontline therapy.[13]

Lymphoblastic lymphoma (LBL), of which the majority are T-cell-lymphoblastic lymphoma (T-LBL), account for 20-25% of the Non Hodgkin lymphoma of childhood and adolescence.[14-16] The on-going protocol of treatment in Europe is the International protocol of the European Inter-group for Childhood Non-Hodgkin Lymphoma (EICNHL) for Lymphoblastic Lymphoma, opened to accrual from 2002. The following figure reports the treatment plan of T-LBL.

Contemporary treatment Protocols show an event-free survival (EFS) that rates in the range of 70% to 80%.[17-19] Outcomes of patients with relapsed/primary refractory T-LBL are poor, but Stem Cell Transplantation (SCT) for these patients could improve EFS.[20]

T-LBL is morphologically and immunophenotypically similar to T-ALL, although T-LBL has minimal marrow involvement (<25% bone marrow blasts). The identification of the patients at risk for early failure is an essential step in designing risk-based therapy in future trials. The kinetics of response is the most important prognostic factor. In T-ALL the leukemic blasts decrease in the bone marrow monitored by means of clone specific probes technology (minimal residual disease monitoring) resulted in an even higher predictive power. In T-LBL due to shortness of diagnostic tumour material, clone specific probes are not always available, therefore this method is difficult to apply in lymphoma patients. In an international cooperation, a consensus panel of antibodies used for minimal residual disease (MRD) monitoring in particular in T-cell acute lymphoblastic leukaemia has recently been accepted. According to pilot observations, this panel can also be adopted for T-LBL. Therefore the technique of MRD monitoring could also be used to estimate the presence of minimally disseminated disease in blood and bone marrow of patients with clinically localised T-LBL. At the moment a pilot-study concerning MRD monitoring of children with T-LBL is ongoing. Future studies could be designed to specifically relate T-ALL and T-

LBL using FISH probes more specific to these tumors, and additional studies to further elucidate the molecular abnormalities in T-LBL. In particular oligonucleotide microarray and/or array comparative genomic hybridizations, may correlate with aberrant protein expression and help better elucidate the molecular pathogenesis of childhood T-LBL.

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