chromosome positivity, and a lower incidence of enlarged lymph nodes or liver. Patients >10 years of age have a 10-15% risk for avascular necrosis of bone and the risk increases with age at diagnosis. Leukemic cells from patients with B-precursor ALL show increased in-vitro drug resistance to prednisone and daunorubicin compared to cells from younger patients.

Two recent studies have shown that adolescents treated on pediatric leukemia trials have a better EFS than similar adolescents treated on adult leukemia trials. EFS on the pediatric trials was approximately 65% at 5 years compared to 40% for adult trials. The reasons for the large EFS differences are not readily apparent. Treatment protocol, actual drug intensity, compliance with therapy, and supportive care practices should be evaluated in an effort to explain the EFS differences.

In the most recent Children's Cancer Group (CCG) ALL Protocol 1961, adolescents >10 years of age received a four-drug induction with vincristine, prednisone, L-asparaginase, and daunomycin. A Day 7 bone marrow was performed: patients with ≤ 25% blasts were considered rapid early responders, while patients with >25% blasts were considered slow responders. Rapid early responders were randomized to standard or increased treatment intensity during consolidation, interim maintenance (IM), and delayed intensification phases (DI), and to receive one or two IM/DI combinations. Slow early responders received increased treatment intensity and 2 IM/DI phases (augmented BFM). The four-year EFS for patients 16-21 years of age (N=253) is 72.5%. A new protocol is being developed by the Children's Oncology Group (COG), which will accrue patient up to 30 years of age. A number of adult cooperative groups have shown interest in participating.

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Childhood ALL: from the randomized clinical trials to an evidence-based approach.

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Childhood ALL is a relatively rare disease in which a remarkable progress has been achieved in the last three decades, with approximately a 75% Event Free Survival at 5 years from diagnosis.

The randomized clinical trials (RCTs) have been one of the major factors responsible of the therapeutic progress in the last 20 years. The strategy of RCTs became more complex due to the modest improvement that can be expected in outcome. Problems to be considered are: number of patients, selection of appropriate questions, time to get final results. Large international cooperation has become a crucial requirement.

We describe the experience in RCTs of I-BFM-SG (International BFM Study Group) created by H. Riehm in 1986.

A. 1989-1991: Intermediate Risk ALL: use of the same backbone protocol with different randomizations in different countries (Germany and Austria, Italy, The Netherlands, EORTC – centers from Belgium and France).

B. 1995: large international cooperation applying prospective meta-analysis to evaluate the VCR-Dexamethasone pulses in maintenance (Germany and Austria, Italy, Argentina, Chile, Hungary, Czech Republic).

C. For the first time use of the same protocol in some European countries (Germany, Austria, Switzerland, Italy) to evaluate the impact of Minimal Residual Disease (MRD) and 4 randomized questions.

D. Large international cooperation (Czech Republic, Chile, Uruguay, Argentina, Croatia, Poland, Hong Kong, Hungary, Israel) asking the same questions as in C. without MRD stratification.

A contribution to a better selection of the more relevant questions to be included in RCTs is the use of the so-called "retrospectoscope" (JCO 1997; 15: 1289-90) the critical evaluation of the information available in the literature from RCTs as well as from observational studies.

One example is presented: the TIT vs MTX alone for CNS preventive therapy has been introduced in 1971. In 2003 only, after a RCT performed by CCG, a clear conclusion has been obtained.