Pediatric Congenital Hematologic Disorders Research Center
مرکزتحقیقات بیماری های خونی مادرزادی کودکان

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M R D

When? How?

Standard risk ALL (and its exceptions

- WBC at diagnosis below 50×109/L
- - age <10 years but > 1 year
- - no central nervous system (CNS) involvement
- - *ETV6/RUNX1 positivity*
- - MRD at Day 15 of induction therapy < 0.1%
- - MRD at end of induction negative (if sensitivity
- reaches at least 10-4)

Hyperdiploid ALL

- there are high-risk patients (defined by high levels of MRD at end of induction-consolidation which is approx. 12 weeks from diagnosis) even among hyperdiploid cases as much as among patients with *ETV6/RUNX1 positivity due to* their slow response to treatment. They are characterized by residual disease at a level of 10-3 or higher at 12 weeks from diagnosis if treated on this regimen

Intermediate-risk ALL

- T-precursor cell ALL6
- - t(1;19)4,8
- - iAMP21
- - CNS involvement and/or traumatic lumbar puncture
- - WBC ≥50×109/L
- - age ≥10 years
- - age <1 yea

- the prognostic relevance of high WBC as much as for the two age groups listed here depends largely on the response to treatment as measured early by the prednisone response in peripheral blood, or in bone marrow Day 15

High-risk ALL

- t(9;22) or *BCR/ABL1 present*
- t(4;11) or *MLL rearrangement present*
- hypodiploidy (modal chromosome number below 45 chromosomes)
- induction failure
- inadequate early response:
- -'prednisone poor response' >1000 blasts in peripheral blood at Day 8 of therapy
- -M3 marrow at Day 7 or Day 14 of induction therapy
- -by MRD detection on Day 8, Day 15, and Day 28-33 of induction therapy (this applies in particular for pcB-ALL)
- - slow response: persisting high levels of MRD at the end
- of induction-consolidation (week 12) or even later

- *MLL aberrations* or *BCR/ABL1*
- The use of MRD monitoring in the AIEOP-BFM ALL 2000 trial revealed that there are Ph+ALL patients who are fast responders, and so have already cleared residual disease at the end of the 5-week induction therapy, and they have an excellent outcome.

- Gene expression profiles in precursor B-cell ALL have been described which are eminiscent of that in Ph+ ALL and are associated with a poor prognosis

The clinical need for novel therapies

- to improve risk stratification for better adaptation of treatment intensity
- to investigate if the previously established system of early *in vivo response analysis (by MRD detection)* can be further refined through panels of molecular markers at time of diagnosis;
- to evaluate the therapeutic benefit of alternativeapproaches such as immunotherapy and/or allogeneic hematopoietic stem cell transplantation in patients refractory to conventional treatment.

- **Time point-dependent concordance of flow cytometry and real-time quantitative polymerase chain reaction for minimal residual disease detection in childhood acute lymphoblastic leukemia**

- *Haematologica 2012;97(10):1586-1593. doi:10.3324/haematol.2011.060426*

Time point-dependent concordance of flow cytometry and real-time

- **Conclusions**
- Within the current BFM-based protocols, flow cytometry and polymerase chain reaction cannot simply substitute each other at single time points, and the concordance rates between their results depend largely on the time at which they are used. Our findings suggest a potential complementary role of the two technologies in optimizing risk stratification in future clinical trials.

Pognostic significance and modalities of flow cytometric minimal residual disease detection Blood.2002 99: 1952-1958

- **Sequential monitoring at day 33 and week 12 on BM was most useful for predicting outcome independently from clinical risk groups:patients with persistent disease (> 1 blast/mL) had a 100% probability of relapse, compared to 6% in all others.**
- d 15
- d 33
- wk 12
- wk 22-24

- **Minimal residual disease in peripheral blood at day 15 identifies a subgroup of childhood B-cell precursor acute lymphoblastic leukemia with superior prognosis**

- *Haematologica 2011;96(12):1815-1821. doi:10.3324/haematol.2011.042937*

Minimal residual disease in peripheral blood at day 15 identifies …

- real-time quantitative polymerase chain reaction analysis to examine minimal residual disease in 398 pairs of blood and bone marrow follow-up samples from 95 children with B-cell precursor ALL
- At day 15, a level of MRD in blood lower than 10-4 was associated with an excellent 5-year relapse-free survival in 78 investigated patients (100% *versus 69±7%; P=0.0003).*Subgroups defined by the level of minimal residual disease in blood at day 15 (high-risk: ≥10-2,intermediate-risk: <10-2 and ≥10-4, standard-risk: <10-4) partially correlated with bone marrow based stratification described previously, but the risk groups did not match completely
- added prognostic information to the risk stratification based on minimal residual disease at day 33 and week 12.

- Clinical significance of minimal residual disease in childhood acute lymphoblastic leukemia and its relationship to other prognostic factors: a Children's Oncology Group study

- *Blood First Edition paper, April 3, 2008; DOI 10.1182/blood-2008-01-132837*

Day-29 marrow MRD was the most important prognostic variable in multivariate ...

- by flow cytometry in the peripheral blood at day 8, and in end-induction (day 29) and endconsolidation marrows in 2143 children B ALL
- The presence of MRD in day-8 blood and day-29 marrow MRD was associated with shorter event-free survival (EFS) in all risk groups; even patients with 0.01% to 0.1% day-29 MRD had poor outcome compared with patients negative for MRD patients (59% 5% vs 88% 1% 5-year
- EFS).

- **Day-29 marrow MRD was the most important prognostic variable in multivariate analysis**

- **The 12% of patients with all favorable risk factors, including NCI risk group, genetics, and absence of days 8 and 29 MRD, had a 97% plus or minus 1% 5-year EFS with nonintensive therapy. T**

- Molecular response to treatment redefines all prognostic factors in children and adolescents with B-cell precursor acute lymphoblastic leukemia:results in 3184 patients of the AIEOP-BFMALL 2000 study
- February 12, 2010; DOI 10.1182/blood-2009-10-248146

- **Patients with precursor B (pB) ALL (n 3184) were considered MRD standard risk (MRD-SR) if MRD was already negative at day 33 (analyzed by2 markers, with a sensitivity of at least 104);MRD high risk (MRD-HR) if 103 or more at day 78 and MRD intermediate risk (MRD-IR):others.**

- **MRD-SR patients were 42% (1348):5-year event-free survival (EFS, standard error) is 92.3% (0.9). Fifty-two percent (1647) were MRD-IR: EFS 77.6% (1.3). Six percent of patients (189) were MRD-HR: EFS 50.1% (4.1; *P* < .001).**

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- **PCR-MRD discriminated prognosis even on top of white blood cell count, age, early response to prednisone and genotype. MRD response detected by sensitive quantitative PCR at 2 predefined TPs is highly predictive for relapse in childhood pB-ALL.**