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Minimal residual disease after induction is the strongest predictor of prognosis in intermediate risk relapsed acute lymphoblastic leukaemia – Long-term results of trial *ALL-REZ BFM P95/96*

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Abstract ***Purpose:*** This blinded prospective study was performed to optimise the risk assessment of children with a late isolated, combined or an early combined bone marrow (BM) relapse of precursor B-cell acute lymphoblastic leukaemia (ALL). The aim was to develop a reliable tool to identify patients with an intermediate risk relapse who are in need of haematopoietic stem cell transplantation (HSCT).

Methods: Included were 80 children and adolescents with first intermediate risk BM relapse of ALL recruited in trial *ALL-REZ BFM P95/96*. We assessed the prognostic value of minimal residual disease (MRD) after induction therapy quantified by PCR using leukaemia clone-specific T-cell receptor/immunoglobulin gene rearrangements.

Results: Molecular good responders (MRD $< 10^{-3}$, $n = 46$) had a probability of event-free survival (pEFS) at 10 years of 76% standard error (SE) ± 6% and a cumulative incidence of second relapse (CIR) at 10 years of 21% SE ± 6%; pEFS of molecular poor responders (MRD $\geqslant 10^{-3}$, $n = 34$) at 10 years was 18% SE ± 7% and CIR 61% SE ± 9% ($p < 0.001$). Cox regression analysis revealed MRD after induction to be the strongest independent prognostic parameter with a 6.6-fold increased risk (95% confidence interval 3.3–13.5, $p < 0.001$) for molecular poor responders to suffer a subsequent adverse event compared to good responders.

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Conclusion: In patients with intermediate risk BM relapse of ALL, low MRD after induction is associated with an excellent long-term prognosis with conventional chemo-/radiotherapy whereas patients with insufficient response have an extremely poor prognosis. Therefore, in the subsequent trial *ALL-REZ BFM 2002*, MRD is used to allocate molecular good responders to conventional post-induction therapy and molecular poor responders to allogeneic HSCT.

1. Introduction

Children having experienced a relapse of acute lymphoblastic leukaemia (ALL) require a second round of treatment which is often more aggressive than frontline treatment. Therefore, there is a particular need to reliably assess the risk for a subsequent relapse and to allocate patients to treatment regimens with adequate intensity and justifiable toxicity.[1–3]

In the experience of the BFM (Berlin, Frankfurt and Münster) study group, time to relapse, site of relapse and ALL-immunophenotype have been established as the most important prognostic determinants to stratify patients with first relapse into different treatment groups.[4–6] Similar stratification criteria have been used in other trials.[2,7]

One of the most critical questions in relapsed ALL treatment has not been resolved and concerns exist whether intensified therapy such as allogeneic haematopoietic stem cell transplantation (HSCT) is required to achieve long-term control of leukaemia.[8] For patients with a very early (<18 months after diagnosis) or early (between 18 months after diagnosis and 6 months after cessation of frontline chemotherapy) isolated bone marrow (BM) relapse, a very early BM/extramedullary combined relapse or all T-cell ALL with BM involvement at relapse diagnosis, it has been clearly shown that nearly all suffer a subsequent relapse when being treated solely with conventional intensive post-induction chemotherapy.[6] For this high-risk group, allogeneic HSCT has therefore been established as standard post-induction therapy. Conversely, the probability of event-free survival (pEFS) of late isolated extramedullary relapses is in the range of 70% achieved by polychemotherapy (and localised treatment, if appropriate) not justifying HSCT.[3] Between both groups, the intermediate risk group comprising more than 50% of patients represents the most heterogeneous risk group among patients with first ALL-relapse.[3] This group includes patients with B-cell precursor (BCP) ALL with either late (>6 months after cessation of frontline chemotherapy) isolated BM relapse, or with a late or early combined BM/extramedullary relapse as well as all early or very early isolated extramedullary relapses.

Early response to therapy has been shown to be of high prognostic significance in childhood ALL. The most reliable and sensitive tool to assess this response is the measurement of minimal residual disease (MRD) by polymerase chain reaction (PCR) using clone-specific T-cell receptor (TCR)/immunoglobulin (IG) gene rearrangements or by flow-cytometry.[9–15] Our group demonstrated in a first retrospective study the prognostic significance of MRD in childhood relapsed ALL,[16] which has been confirmed by other reports.[17,18] However, in these studies patient numbers were small, the risk groups were not uniformly defined and the observation times were rather short. Furthermore, there was no homogenous relapse treatment within the studied cohorts, and only one study performed a multivariate analysis.[16–18]

We performed a prospective blinded study of the prognostic value of MRD after induction therapy in 80 uniformly treated intermediate risk patients with microscopic BM involvement at relapse diagnosis. The aim was to reliably assess the prognostic significance of MRD, to determine the adequate MRD cut-off and, thus, to establish a valid basis for stratification strategies in subsequent trials.

2. Methods

2.1. Patients and samples

Patients of the intermediate risk group (S2) with cytologically proven BM involvement at relapse diagnosis were included in the study, i.e. in the case of an isolated BM relapse $\geqslant$25% and of a combined relapse $\geqslant$5% of leukaemia cells in BM. According to the S2-group definitions these patients had either an early combined, a late combined or isolated BM relapse of BCP-ALL. Additionally the following inclusion criteria had to be met: (1) first relapse, (2) treatment according to the *ALL-REZ BFM P95/96* protocol, (3) complete cytological remission after induction, (4) younger than 18 years at relapse diagnosis, (5) adequate BM aspirates at first relapse diagnosis and after the induction phase.

The included patients were diagnosed with a first relapse during the time period from 01/07/1995 until 31/12/2001. The median observation time for patients in continuous complete remission (CCR) was 10.4 years (range: 8.9–15.4).

The patients used for the analysis of representativeness met the same inclusion criteria except of (5) and