Challenges and controversies in pediatric acute lymphoblastic leukemia

Treatment of childhood acute lymphoblastic leukemia

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INTRODUCTION

Biological features at diagnosis of ALL such as patient age, WBC, organ involvement, immunophenotype, and cytogenetics have been used by all major study groups to stratify treatment composition and intensity. Recently, treatment intensity has turned out to be also a major prognostic factor (Reiter et al. 1994; Schorin et al. 1994; Chessells et al. 1995; Pui 1995; Nachman et al. 1998; Schrappe et al. 2000). The BFM group has addressed the impact of treatment intensity already in randomized trials ALL-BFM 81 and 83 conducted from 1981 to 1986 (Riehm et al. 1987; Schrappe et al. 1987; Schrappe et al., 2000a). The importance of delayed reintensification was confirmed in trial ALL-BFM 86 (Reiter et al. 1994). The prognostic influence of early treatment response was prospectively evaluated in trial ALL-BFM 83, and later utilized in trials ALL-BFM 86 and 90 to identify a group of ALL patients with the highest risk for relapse (Riehm et al. 1987; Reiter et al. 1994; Schrappe et al. 2000). Various approaches to determine the early *in vivo* response were developed in the last 15 years mainly concentrating on the cytomorphological evaluation of blast cell clearance from the peripheral blood and the bone marrow (Gajjar et al. 1995; Steinherz et al. 1996; Gaynon et al. 1997). Only recently, more sensitive methods of minimal residual disease detection have been applied systematically to evaluate the *in vivo* response (Coustan-Smith et al. 1998; van Dongen et al. 1998). In parallel to recent advances in risk-adaptation of treatment, some important attempts have been made to reduce the toxicity by limiting in particular the components with the potentially most relevant long-term toxicity such as radiotherapy. This paper summarizes the information on prognostic factors in childhood ALL as derived from the ALL-BFM trials, and examines the clinical relevance with respect to future development of treatment strategies.

CLINICAL AND BIOLOGICAL PARAMETERS AT DIAGNOSIS

WBC, age, gender, cytogenetic and immunphenotypic subtypes are the major factors determining the risk of relapse (Tab. 1). To determine the risk of relapse it is useful to rely on parameters which are always available and not subject to methodological variations. Age and WBC are ideal parameters, as these factors are always available. Therefore, standard (SR) and high risk (HR) patients have been defined by age/WBC subsets, e.g. in the classification of the National Cancer Institute: SR, age 1-9 years, and WBC <50,000/mm³; HR, age ≥ 10 years or WBC ≥ 50,000/mm³ (Smith et al. 1996). The BFM group prepared results accordingly, thus demonstrating a 6y-EFS of 86±1% for NCI-SR patients (n=1395), and 64±2% for NCI-HR patients (n=724) in trial ALL-BFM 90 (T-ALL patients included). Infants which were not included in the NCI definition were also analyzed: their 6y-EFS was 50±7% (Schrappe et al. 2000). With regard to the risk groups as defined in trial ALL-BFM 90, 6y-EFS was 85±2, 82±1, and 34±3% for SR (n=636), MR (n=1299), and HR (n=243) patients, respectively. Molecular screening for fusion genes and cytogenetics at diagnosis are useful methods to identify some of the high risk patients, but the majority

of the patients at risk will not be recognized (Schlieben et al. 1996).

RESPONSE EVALUATION

Early response to prednisone

Analysis of response to treatment in peripheral blood after 7 days of PRED and one IT injection of MTX which had prospectively been evaluated in trial ALL-BFM 83 (Riehm et al. 1987) identified a novel poor prognostic marker that was more predictive of relapse than any other marker used thus far: 8% of the patients formed a small poor risk group that was characterized by the presence of ≥1000 leukemic blasts per µl peripheral blood after the first week of prednisone (PRED-PR). After a median observation time in trial ALL-BFM 83 of 10 years the probability for event-free survival (pEFS) for patients with PRED-PR is 39%, compared to 66% in patients with adequate response to prednisone. No other mathematical model nor any other single factor could describe a group of patients that was as large, and had a prognosis of less than 50% pEFS (Tab. 1). Reflecting the reliability of this method 8-10% of the patients have always been identified as PRED poor responders in all three BFM trials since 1983. In addition, some characteristics have constantly been observed in these trials (Riehm et al. 1987; Reiter et al. 1994) that indicate that this parameter is associated with some well known poor risk features (Tab. 2). Any treatment variation or intensification that was applied in trials ALL-BFM 86 and 90 for patients with PRED-PR did not significantly alter the outcome of this group (Schrappe et al. 2000). In trial ALL-BFM 95, however, significant improvement for patients with PRED poor response has been demonstrated: 56±4% vs. 32±3% in trial ALL-BFM 90 (unpublished data). Other study groups also utilized the prognostic significance of blast cell reduction in PB or BM (Arico et al. 1995; Gajjar et al. 1995; Gaynon et al. 1997; Nachman et al. 1998).

Table 1: Prognostic factors in patients with childhood acute lymphoblastic leukemia

	Favorable	Unfavorable
Age at diagnosis (y)	≥ 1 and < 10 years	< 1 or ≥ 10 years
Sex	Female	Male
WBC[1] at diagnosis (x10⁹/lL)	< 50	≥ 50
Immunophenotype	common ALL	pro B-ALL, T-ALL
CNS disease[2]	no (CNS 1)	yes (CNS 3)
Genetic features[4]	DNSA index[3] > 1.16, TEL/AML1 positivity, hyperploidy	DNSA index ≤ 1.16, hypoploidy, t(9;22) or BCR/ABL positivity, t(4;11) or MLL/AF4 positivity
Early response to treatment (peripheral blood)	< 1 x 10⁹/lL blood blasts after 7 days of prednisone and a single intrathecal dose of methotrexate on treatment day 1	≥ 1 x 10⁹/Ll blood blasts after 7 days of prednisone and a single intrathecal dose of methotrexate on treatment day 1
Early response to treatment (bone marrow)	< 5% leukemic blasts in the bone marrow (M1) on day 7 and day 15 of induction treatment	> 25% leukemic blasts in the bone marrow (M3) on day 7 and/or day 15 of induction treatment
Remission status after induction therapy	remission bone marrow (M1) (BFM: on treatment day 33)	non-response to treatment (≥ 5% blasts in the bone marrow: M2 or M3) after induction on treatment day 33

[1] white blood cell count;
[2] patients with CNS 2 status (presence of blasts but less than 5 cells/µL) fared as wellas CNS 1 patients both in trials ALL-BFM 90 and 95;
[3] DNA index of the leukemic blasts is defined as the ratio of DNA content in leukemic G0/G1 cells to that of normal diploid lymphocytes;
[4] either assessed by flow cytometry, cytogenetic techniques or molecular genetic techniques

Table 2: Outcome by prednisone good-response and prednisone poor-response in specific patient subsets: Data from recent ALL-BFM trials

	Prednisone No. of patients	Good-Response % EFS ± SE[1]	Prednisone No. of patients	Poor-Response % EFS ± SE[1]
NCI risk group[2]				
Standard risk	1324	87 ± 1	48	45 ± 7
High risk	564	73 ± 2	143	31 ± 4
Immunophenotype				
Pro-B ALL	80	68 ± 6	19	0
Common ALL	1274	84 ± 1	67	46 ± 6
Pre-B ALL	338	79 ± 2	13	31 ± 13
T ALL	180	78 ± 3	101	32 ± 5
Genetic aberrations				
t(9;22) or BCR/ABL pos.	37	55 ± 8	20	10 ± 7
Infants				
all infants	78	53 ± 6	27	15 ± 7
infants with 11q23 rearrangement	17	41 ± 12	11	9 ± 9
infants t(4;11) or MLL/AF4 positive	9	33 ± 16	7	0 ± 0

[1]Percent event-free survival ± standard error
[2]For explanation of NCI risk groups see Smith, M. et al.

Response in the Bone Marrow

Since 1990, BM on day 15 of therapy has been routinely evaluated in the central laboratory of the ALL-BFM trial. The evaluation of the BM slides was associated with more technical problems than the evaluation of blood smears, and low cellularity often prevented conclusive results. In addition, the specificity of the BM evaluation was limited: The same number (not percent!) of relapses was observed among patients with a M1, or a M2, or a M3 marrow on day 15. Nevertheless, a M3 marrow (found in 13% of patients) was an indicator of high relapse risk, as 6y-EFS was only 44±5%. Among patients with PRED-GR, an M3 marrow was demonstrated in 7.3% of the patients, with an EFS of 54±7%. Failure to achieve remission as shown by a M2 or M3 BM at control time (in BFM, day 33 of induction), was the most adverse prognostic factor in trial ALL-BFM 90, as 6y-EFS was only 11±5% for such patients. This poor risk subset comprises, however, only 2.5% of all patients (Tab. 2).

Response as assessed by evaluation of minimal residual disease (MRD)

Highly sensitive, clonospecific detection of MRD during treatment of ALL has been shown to provide a new tool for prognostic evaluation of patients with childhood ALL (Foroni et al. 1997; Seriu et al. 1997). A collaborative study of four laboratories within the International BFM Study Group identified three distinct risk groups on the basis of semiquantitative MRD determination at 5 and 12 weeks of therapy (van Dongen et al. 1998). This approach identified two thirds of the relapses within the newly defined high risk group but virtually no failures within the large group of patients (40%) with fast clearance of leukemic blasts.

KEY ELEMENTS OF TREATMENT

In addition to the major prognostic impact of a multidrug induction regimen which formed the basis of success, several other key elements of therapy have been identified over the last 25 years, the most important one being the delayed reintensification (reinduction with "Protocol II"). Allogeneic bone marrow transplantation which was introduced for highly selected high risk patients in the late 80s still has only a limited overall impact on cure rate for childhood ALL. In some subsets such as Ph+ ALL the benefit has been demonstrated (Schrappe et al., 1998a). Recent data from trial ALL-BFM 95 suggest that the outcome for the rather large group of unfavorable T-cell ALL (characterized by PRED-poor-response) can be improved by allogeneic BMT (unpublished data).

Reinduction therapy

In trial ALL-BFM 83, 126 patients with standard-low risk (SR-L) ALL (BFM-RF <0.8, no initial CNS disease: WBC <10,000 in 95%; only approx. 25% of the patients being older than 10 years) were randomized to receive or not to receive reinduction therapy with *Protocol III* (details in ref. (Schrappe et al. 1987)). Reinduction therapy was scheduled to start two weeks after the end of consolidation therapy, that is 23 weeks after diagnosis (arm SR-L/2). Patients randomized not to receive reinduction therapy (SR-L/1) were started on maintenance therapy with oral 6-MP and MTX two weeks after consolidation (Riehm et al. 1987; Schrappe et al. 1987). Omitting reinduction increased the relapse rate 2.5-fold from 17% to 41%, resulting in an EFS of 59±6% for patients treated without reinduction, and 83±5% for patients who did receive reinduction. This result was reproduced in the initial cohort of standard risk patients in subsequent trial ALL-BFM 86 in which even the introduction of high-dose methotrexate in consolidation could not prevent this high rate of relapses (Reiter et al., 1994, Schrappe et al., 2000a). The majority of relapses was systemic recurrences. Since 1988, however, intensive reinduction therapy is a key element of BFM therapy also for all standard risk patients.

Maintenance therapy: Treatment duration

764 patients irrespective of their risk features were randomized in trials ALL-BFM 81 and ALL-BFM 83 for 18 vs. 24 months of total therapy duration. All other patients (n=345) were chosen for one or the other treatment arm (145 patients for 18 months, 200 patients for 24 months). All events prior to the 18th month of therapy were censored in this analysis. Thus, the probability for event-free interval (pEFI) is 79% after a medium observation time of 10 years (range 8-12 yrs) for patients randomized for 24 months, but only 71% for patients randomized for 18 months (p=0.0097). The majority of late relapses occurred in patients with B-precursor ALL, thus, extended maintenance therapy could prevent a significant portion of relapses in that subgroup: pEFI is 72% for 24 months, vs. 62% for 18 months (p=0.01). In contrast, patients with T-ALL rarely experienced a relapse more than 18 months after diagnosis.

Consolidation phase

Since trial ALL-BFM 86, high-dose methotrexate (HD-MTX) with 5 grams per m^2 given in 24h (four cycles) has been introduced into the consolidation phase, and has replaced intermediate dose MTX ($0.5g/m^2$). The aim was to control extramedullary, in particular CNS, recurrences and to allow elimination or reduction of preventive radiotherapy. CNS relapses were controlled by this approach very effectively, as in trial ALL-BFM 90 only 1.0% isolated, and 1.9% combined CNS relapses have been observed while preventive cranial radiotherapy (12 Gy) was applied only in medium and high risk patients (Schrappe et al. 2000).

The major advantage of HD-MTX was demonstrated for T-ALL patients with adequate response to prednisone: EFS improved from 58±7% (trial ALL-BFM 83) to 82±4% and 78±3% in trials BFM 86 and 90, respectively (p=0.002). In T-cell lymphoblastic lymphoma the introduction of HD-MTX was certainly an important contributing factor in improving the outcome to 90% EFS (Reiter et al. 2000). Due to the high efficacy towards CNS-protection, the use of HD-MTX also allowed to omit IT MTX in maintenance therapy in contrast to the treatment schedules of many ALL study groups.

Preventive cranial radiotherapy (pCRT)

Since trial ALL-BFM 81, the BFM group systematically tried to reduce or eliminate preventive cranial radiotherapy in children with ALL. The first attempt to replace pCRT by intermediate dose MTX failed in trial ALL-BFM 81 (Schrappe et al. 1998b and 2000a). Subsequently, it was demonstrated that 12 Gy was as effective as 18 Gy for pCRT (Schrappe et al. 2000). In the last trial ALL-BFM 95, 12 Gy has only been applied in T-cell ALL and HR patients. Preliminary analysis indicates that no significant increase in CNS-related relapses was observed (unpublished results).

Treatment mortality

Early mortality in ALL-BFM trials 83 to 90 ranged between 0.3% and 1.7% of patients with the main causes for treatment-related fatalities being infections during neutropenia, occasionally combined with organ dysfunction. With regard to post-remission toxicity, a fatality rate of 1.3% and 1.6% was noted in trial ALL-BFM 86 and 90, respectively (Reiter et al., 1994; Schrappe et al. 2000). These fatalities were mainly due to infectious complications but also to bleeding and organ failure. The described mortality observed in BFM trials is comparable to mortalities observed in trials by other study groups.

TREATMENT OF RELAPSE

The treatment success of ALL relapse very much depends on time of relapse and subtype of leukemia.

Modifications of chemotherapy has improved the overall result in most subsets. Allogeneic BMT from a matched family donor is considered now a beneficial part of treatment.

DISCUSSION

The prognostic significance of leukemia specific biological factors is undoubted, therefore, initial diagnostic procedures have to aim at obtaining as much information as possible to use the combination of immunological, cytogenetic, and moleculargenetic findings for optimal risk adjustment of therapy. Especially in large multicenter trials, however, there are technical and logistic limitations to retrieve all these informations from all patients. With the exception of rather rare, well-defined cytogenetic abnormalities, easily available factors such as WBC, age and sex have also successfully been used for risk assessment (Tubergen et al. 1993b; Schorin et al. 1994b; Chessells et al. 1995b). Analysis of early therapy response has provided an additional instrument to detect increased risk of failure in ALL therapy (Riehm et al. 1987; Gaynon et al. 1990). It was also shown that this rather simple and universally applicable tool was even effective in the well-characterized subset of ALL patients with t(9;22) (Schrappe et al. 1998a) and in infant ALL (Doerdelmann et al., 1999).

All risk parameters have to be investigated for their overall prognostic relevance. This means that identification of a rare biological factor which correlates with a poor prognosis might not be very relevant for the total cohort, as group outcome will not change much even when patients with that parameter can be treated more adequately. On the other hand, if the unfavorable subset of a given parameter comprises a large number of recurrences, new and more effective therapy might improve overall outcome substantially. In addition, if a parameter such as high persistent level of MRD is highly specific and is correlated with a dismal prognosis, it is justified, even mandatory, to develop experimental therapies. Such a rational approach in utilizing the specificity of response parameters (including MRD evaluation) has been initiated now by a large multicenter trial of the AIEOP and BFM ALL Study Groups in Germany, Austria and Italy. This study will still include the - successful - principle of over-treatment but it will attempt to limit the over-treatment in a large, well-defined subset of patients to avoid the late effects which were previously and are still currently found in children treated for ALL. A very similar approach is taken by a new trial of the International BFM Study Group in which response in PB and BM at three time points of induction forms the basis for stratification into three risk groups.

The next trial of the ALL-BFM relapse study group (chair: G. Henze, Berlin) is also planning to use the information on MRD after the first two induction pulses for further treatment stratification in the largest group of patients with not-early non-T cell ALL relapse („S2").

Treatment intensity is well known to have a major impact on event-free survival in leukemia treatment (Riehm et al. 1990; Sallan et al. 1990; Rivera et al. 1991; Gaynon et al. 1993; Reiter et al. 1994; Schorin et al. 1994; Chessells et al. 1995). Two randomized trials of the ALL-BFM group demonstrated that rather late intensification of treatment is effective in preventing some subsequent relapses. First, extension of the maintenance therapy from 18 to 24 months can decrease the rate of relapses for both sexes by approx. 7%. The advantage was independent of the initial BFM risk factor but limited to patients with B-precursor ALL. This result was not impaired by any increase in toxic events. Secondly, late intensification is indeed important in low-risk ALL patients which limits the possibilities to eliminate mulitdrug regimen (Riehm et al. 1987; Tubergen et al. 1993). More recently, we were able to demonstrate in a large number of patients that increased dose intensity in induction can reduce the relapse rate in intermediate risk patients despite reduction of anthracyclines and pCRT (Schrappe et al. 2000 and 2000a).

It is quite easily possible to describe a low-risk group and a high-risk group in childhood ALL, but the characteristics of the intermediate or medium risk group that predict treatment failure are more difficult to define. The majority of relapses in an unselected group of patients will occur in individuals that were not previously identified of having special risk features as patients in the high risk group: In trial ALL-BFM 86, 135 (58%) of 233 relapses (in 998 patients enrolled) occurred in medium risk patients whereas 60 (25%) occurred in standard risk and 38 (16%) in high risk patients. Identification of new genetic markers of aberrant drug metabolism as well as the functional understanding of resistance to chemotherapy are interesting approaches to prevent the large number of 'unpredictable' relapses by better understanding the 'host'.

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