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Outcome of children and adolescents with relapsed acute lymphoblastic leukaemia and non-response to salvage protocol therapy: A retrospective analysis of the ALL-REZ BFM Study Group

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ABSTRACT

Aim of the study: Non-response (NR) to treatment of childhood relapsed acute lymphoblastic leukaemia (ALL) is an end-point of protocol therapy. Subsequent management has not yet been standardised. This study analyses different approaches after NR to aid optimising future strategies.

Patients and methods: Ninety-three children with NR to treatment according to ALL relapse-protocols of the Berlin/Frankfurt/Muenster (BFM) Study Group (03/1990–2006/1999) were retrospectively assigned to a curative (C: intensive polychemotherapies, stem cell transplantation (SCT); $n = 51$), palliative (P: 1–2 antineoplastic agents; $n = 23$) or supportive (S: no antineoplastic therapy; $n = 19$) treatment approach.

Results: Median survival after diagnosis of NR were 121 (C), 89 (P) and 42 (S) days, respectively ($p < 0.001$). In cohort C, a complete remission (2ndCR) was obtained in 16/51 patients, among these 13 only after SCT, and nine children achieved partial remission. Ten of the 51 patients died from treatment-related complications, 39/51 from disease progression. Today, two patients are still in continuous CR after SCT. Adverse prognostic factors were overrepresented in the non-curative cohorts. Time-point of relapse and treatment after NR were independent predictors of survival duration. Most patients without antineoplastic treatment died at home, the majority of the others in the hospital.

Conclusions: Treatment after NR has been heterogeneous and customised. Therapies with curative intent are capable of inducing 2ndCR but associated with high treatment-related morbidity, -mortality and minimal survival. NR patients may, therefore, be ideal candidates for controlled phase I/II trials, thus offering them a chance to benefit from new drugs and promoting drug development for cohorts with better prognosis.

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1. Introduction

With current protocols, survival rates of ~80% can be achieved for children with acute lymphoblastic leukaemia (ALL).[1] Nevertheless, prognosis is substantially reduced in case of relapse.[2,3]

Since 1983, the outcome of children with first ALL-relapse was improved by trials of the ALL-Relapse Berlin/Frankfurt/Muenster (ALL-REZ BFM) group using risk-adapted, multiagent chemotherapy regimens[4–8]and conducting stem cell transplantation (SCT) for high-risk (HR) patients in second complete remission (2ndCR).[8,9] Rates of 85% for 2ndCR and 30–40% for continuous CR (CCR) were reported.[5–8,10,11] About 50% in 2ndCR later on suffered a subsequent relapse and others did not achieve a 2ndCR.[2,12,13] For these patients with non-response (NR) to relapse-protocol-therapy, no standardised management-algorithm has been developed yet.

NR to ALL-REZ BFM regimens may result from a resistant type of leukaemia that has shown to be not curable so far[2] and thus leads to cessation of protocol-therapy. The struggle of patients, families and physicians to cope with this situation often results in further treatment with curative intention. Hence, intensive and expensive therapies are performed, the prognostic impact of which has, to our knowledge, not been analysed yet.

We analysed 93 patients with NR to treatment according to ALL-REZ BFM trials 90[7,8] and 95/96.[11] Our study aimed at (a) classifying treatment concepts after NR, (b) comparing their efficacy and impact on quality of life, and (c) evaluating prognostic factors for future management.

2. Patients and methods

2.1. Patients

From 13th March 1990 to 30th June 1999, 1104 patients younger than 19 years with a first relapse of B-cell-precursor or T-cell ALL were treated according to protocols ALL-REZ BFM 90[7,8], 95/96[11], P91, 92 and 94[14–16] in Germany, Austria, Switzerland, The Netherlands, Denmark and Russia. Hospital- and ALL-REZ BFM-documentation of all patients were retrospectively analysed. Ninety-nine of the 1104 children (9%) experienced a NR. Because of insufficient documentation, 6/99 children were excluded from further analysis.

2.2. Definitions and classification of non-responders

Relapses and risk-groups (S1–S4) were defined as described earlier[7,8,11] (Supplemental Table 1). Patients with NR were defined as those not in 2ndCR (<5% bone marrow (BM) blasts in an otherwise normocellular, regenerative marrow without extramedullary disease and regenerative blood counts without blasts) at defined treatment-time-points according to the different relapse-protocols.[7,8,11,14–16] Patients were divided into subgroups based on the intensity of treatment given with the following intentions: *curative (group C)*-to achieve CCR using polychemotherapy, high-dose (HD)-single-agent regimens or SCT, *palliative (group P)*-to delay disease progression without curative intention using one or a maximum of two antileukaemic agents in low to moderate doses, *supportive (group S)*-to reduce disease-related symptoms without antineoplastic agents. For assigning patients treated according to more than one of these strategies, the determining treatment element was that of highest antileukaemic potential.

2.3. Statistical analyses

Differences in the distribution of variables among subgroups were assessed by the Mann–Whitney *U*- or Kruskal–Wallis-test for continuous variables. Exact Fischer-test was used to analyse the independency of two, Pearson-test of more than two qualitative variables. Kaplan–Meier life-table-analysis[17] was performed to present survival data of the total cohort and subgroups only considering disease- or treatment-related deaths as subsequent events. Subgroups were compared by the two-sided log-rank-test. In all tests, two-sided p at 0.05 or higher was regarded as not significant. Multivariate Cox-stepwise-forward-conditional–regression-analysis was done to determine statistically significant independent indicators of outcome. Data were acquired using "Visual dBase IV" and analysed using SPSS 11.0 software.

3. Results

3.1. Patients with NR

Patient characteristics are presented in Table 1. The majority of patients with NR (51/93; 55%) were assigned to group C, followed by group P (23/93; 25%) and group S (19/93; 20%). No significant difference in distribution of relapse-protocols between subgroups was found. Median time between diagnosis of first relapse and withdrawal from relapse-treatment was the longest in group C (63 d). Overall, the time-point of cessation of relapse-protocol-therapy was variable, significantly dependent on relapse-protocol ($p = 0.026$) and strategy group ($p < 0.001$) but not associated with subsequent NR-management (data not shown). Neither *BCR–ABL*-fusion[18] nor other established risk-factors, such as ALL-immunophenotype, time-point or site-of-relapse[2,12] were significantly associated with the NR-approach. However, while HR-patients were significantly overrepresented in the non-curative cohorts, group-C-patients had an initially more favourable prognosis: most of them were assigned to lower risk-groups S2 and S3 and significantly less ($p = 0.013$) to HR-group S4. Overall, the distribution of risk factors among subgroups was inhomogeneous ($p = 0.026$).

3.2. Treatment after NR

Treatment-elements after NR are presented in Table 2.

3.2.1. Group C

Treatment with curative intention was given to 51/93 patients (55%), 41 of whom (80%) received intensive polychemotherapy-courses based on BFM[19,20] and other standardised protocols for treatment of childhood leukaemia. Twenty-two patients underwent SCT, 12 of whom after polychemotherapy.

Table 1 – Frequencies of clinical and prognostic parameters of children and adolescents with first relapse of ALL and non-response (NR) to protocol therapy according to trials ALL-REZ BFM 90[7,8], 95/96[11] and ALL-REZ BFM pilot protocols[14–16] by treatment approach after NR.

Clinical and prognostic parameters of non-responders	Total	Treatment approach after NR Frequencies among subgroups			
		Documented cases without antileukaemic therapy (group S)	Documented cases with palliative approach (group P)	Documented cases with curative approach (group C)	*p*
Total of documented cases: *n*	93 (100%)	19 (20%)	23 (25%)	51 (55%)	
Gender	93 (100%)	19 (100%)	23 (100%)	51 (100%)	
Male	63 (68%)	13 (68%)	14 (61%)	36 (71%)	0.708*
Female	30 (32%)	6 (32%)	9 (39%)	15 (29%)	
Age at relapse [y]: median (minimum; maximum)	8 (1; 18)	10 (4; 17)	8 (1; 18)	8 (2; 18)	0.341#
Log10 PBC/µl: median (minimum; maximum)	2.8 (0; 5.4)	2.8 (0; 4.6)	3.1 (0; 5.4)	2.7 (0; 4.6)	0.415#
Duration of first CR [y]: median (minimum; maximum)	412 (118; 3739)	377 (213; 992)	373 (124; 3566)	491 (118; 3739)	0.070#; 0.023##
Time point of relapse		19 (100%)	23 (100%)	51 (100%)	0.387*; 0.209**
Very early	62 (67%)	16 (84%)	16 (70%)	30 (59%)	
Early	22 (24%)	2 (11%)	5 (22%)	15 (29%)	
Late	9 (10%)	1 (5%)	23 (9%)	6 (12%)	
Site of relapse					0.317*; 0.126**
BM isolated	71 (76%)	13 (68%)	17 (74%)	41 (80%)	
BM combined	17 (18%)	5 (26%)	6 (26%)	6 (12%)	
EM isolated	5 (5%)	1 (5%)	–	4 (8%)	
Immunophenotype	89 (96%)	19 (100%)	22 (96%)	48 (94%)	0.804*
Common ALL	39 (44%)	7 (37%)	9 (41%)	23 (48%)	
Pre-B ALL	10 (11%)	1 (5%)	2 (9%)	7 (15%)	
T/Pre-T ALL	29 (33%)	8 (42%)	7 (36%)	12 (25%)	
Other	11 (12%)	3 (16%)	3 (14%)	5 (10%)	
No data	4 (4%)	–	1 (4%)	3 (6%)	
Risk group[a]	93 (100%)	19 (100%)	23 (100%)	51 (100%)	0.110*; 0.044**
S2	13 (14%)	1 (5%)	2 (9%)	10 (20%)	0.215*
S3	17 (18%)	1 (5%)	4 (17%)	12 (24%)	
S4	63 (68%)	17 (90%)	17 (74%)	29 (57%)	0.026*
BCR–ABL fusion	50 (54%)	12 (63%)	9 (39%)	29 (57%)	
Negative	36 (72%)	8 (67%)	6 (67%)	22 (76%)	0.775*
Positive	14 (28%)	4 (33%)	3 (33%)	7 (24%)	
No data	43 (46%)	7 (37%)	14 (61%)	22 (43%)	
Induction regimen prior to NR	93 (100%)	19 (100%)	23 (100%)	51 (100%)	0.179*
ALL-REZ BFM 90	34 (37%)	4 (21%)	9 (39%)	21 (41%)	
ALL-REZ BFM 95/96	25 (28%)	9 (47%)	7 (31%)	19 (37%)	
P91	2 (2%)	–	2 (9%)	–	
P92	18 (19%)	6 (32%)	4 (17%)	8 (16%)	
P94	4 (4%)	–	1 (4%)	3 (6%)	
Number of chemotherapy courses until cessation of protocol therapy due to NR	91 (98%)	18 (95%)	22 (96%)	50 (98%)	0.345*
1	11 (12%)	4 (22%)	3 (14%)	4 (8%)	
2	29 (32%)	6 (33%)	9 (41%)	14 (28%)	
3	25 (28%)	5 (28%)	4 (18%)	16 (32%)	
4	20 (22%)	3 (17%)	3 (14%)	14 (28%)	
5	4 (4%)	–	2 (9%)	2 (4%)	
6	1 (1%)	–	1 (5%)	–	

Missing values not included.

[a] See Supplemental Table 1. ALL: acute lymphoblastic leukaemia; ALL-REZ BFM: Berlin/Frankfurt/Muenster-Study Group; BM: bone marrow; CR: complete remission; EM: extramedullary; NR: non-response; P91, 92, 94: ALL-REZ BFM-pilot-protocols; PBC: peripheral blast cell count.

* Pearson.

** Pearson: non-curative versus curative.

\# Kruskal–Wallis.

\## Mann-Whitney U: non-curative versus curative.

Table 2 – Frequencies of therapeutic parameters of children and adolescents with first relapse of ALL and non-response (NR) to protocol therapy according to trials ALL-REZ BFM 90[7,8], 95/96[11] and ALL-REZ BFM pilot protocols[14–16] by treatment approach after NR.

Therapeutic parameters after NR	Treatment after NR			
	Frequencies among subgroups			
	Total	Documented cases without antileukaemic approach (group S)	Documented cases with palliative approach (group P)	Documented cases with curative approach (group C)
Total number of documented cases	93 (100%)	19 (100%)	23 (100%)	51 (100%)
SCT	22 (24%)	–	–	22 (43%)
SC-sources: MUD	6 (27%)	–	–	6 (12%)
MFD	14 (64%)	–	–	14 (27%)
Autologous	2 (9%)	–	–	2 (4%)
HLA-status: Identical	11 (50%)	–	–	11 (22%)
Haploidentical	7 (32%)	–	–	7 (14%)
Mismatch	1 (5%)	–	–	1 (2%)
Autologous	2 (9%)	–	–	2 (4%)
	1 (5%)	–	–	1 (2%)
CR prior to SCT: Yes	3 (13%)	–	–	3 (6%)
No	19 (86%)	–	–	19 (37%)
Pretreatment: Polychemotherapy	12 (55%)	–	–	12 (55%)
Conditioning only	10 (45%)	–	–	10 (45%)
Conditioning: TBI + VP16	10 (45%)	–	–	10 (45%)
TBI + other agent	4 (18%)	–	–	4 (18%)
No TBI; RIC [n (% of $n^{no\ TBI}$)]	8 (36%); 3 (38%)	–	–	8 (36%); 3 (38%)
Chemotherapy	79 (85%)	19 (100%)	23 (100%)	51 (100%)
Polychemotherapy*	41 (44%)	–	–	41 (80%)
Single-agent chemotherapy	38 (41%)	–	21 (91%)	17 (33%)
Glucocorticoids	$29 + 22^{SCT\text{-}patients}$ (55%)	–	8 (35%)	$21 + 22^{SCT\text{-}patients}$ (84%)
Cytokines	24 (26%)	–	3 (1%)	21 (41%)
Radiotherapy	19 (20%)	–	–	19 (37%)
TBI	14 (15%)	–	–	14 (27%)
CNS-irradiation	5 (5%)	–	–	5 (10%)
Supportive care	88 (95%)	18 (95%)	22 (96%)	48 (94%)
Median time between cessation of protocol therapy and start of NR treatment [d] (minimum; maximum)**	19 (0; 54)	–	20 (3; 47)	18 (0; 54)

CNS: central nervous system; CR: complete remission; MFD: matched family donor, MUD: matched unrelated donor; NR: non-response; RIC: reduced intensity conditioning; SC(T): stem cell (transplantation); TBI: total body irradiation. For definitions see main text.

* Details can be provided upon request.

** $p = 0.569$ (Mann–Whitney U).

Myeloablative conditioning including total body irradiation (TBI) and single-agent chemotherapy was performed in 14/22, reduced-intensity conditioning (RIC) in 3/22 cases. Grafts were autologous in 2/22, from matched family (MFD) in 14/22 or matched unrelated donors (MUD) in 6/22 patients. Most children (19/22; 86%) were not in 2ndCR when undergoing SCT. Further treatment-elements included single-agent chemotherapy (33%), glucocorticoids (84%), and cytokines (41%). All 51 patients were hospitalised for treatment.

3.2.2. *Group P*

A quarter of all children with NR (23/93) were palliated. Hospitalisation was significantly less than in group C ($p < 0.001$): about half of group P (52%) was treated as out-patients. Ten

children were intermittently hospitalised for disease-related complications or a short palliative chemotherapy.

3.2.3. Group S

Nineteen of 93 children (20%) did not receive any further anti-neoplastic treatment but supportive care including analgesics and/or blood products to reduce disease-related symptoms.

3.3. Treatment efficacy, subsequent events and survival after NR

3.3.1. Group C

As shown in Table 3, less than one third (16/51; 31%) achieved 2ndCR, among these 13 patients (81% of all 2ndCR) only after SCT. Three SCT-patients were in 2ndCR achieved by preceding polychemotherapy. Ten of the 16 patients in 2ndCR (63%), three after polychemotherapy only and 7 after SCT suffered subsequent relapse (Table 4). Most (90%) of the 29 children, who were given polychemotherapy only, did not achieve 2ndCR. More than two thirds (39/51; 76%) died of leukaemia after persisting NR. Median survival after cessation of relapse-treatment was 121 days. The 16 patients, who achieved a 2ndCR had a median survival of 255 d after diagnosis of NR. Ten of these later on suffered treatment-related deaths – four after SCT with TBI/VP16-conditioning, six after intensive chemotherapy alone. Six patients survived longer than 1 year, resulting in a 1-year-survival rate of 12%. Two boys with NR to protocol-therapy of early isolated non-T-lineage BM- relapses are still in CCR. For NR-management, one received MFD–SCT in 2ndCR (induced by polychemotherapy according to protocol ALL BFM 95[11] and myeloablative conditioning). Seven years later, however, he was still suffering from chronic graft versus host disease (gvhd). The other longterm survivor was not in CR, when receiving MFD–SCT after TBI/VP16- conditioning. No severe longterm side-effects have been documented for him so far.

3.3.2. Group P

No palliated patient achieved a 2ndCR (Table 3). All patients died from leukaemia after NR (Table 4). Median survival was 89 days after cessation of relapse therapy. The 1-year-survival rate was 4%.

3.3.3. Group S

All children of group S died from leukaemia. Median survival was 42 days after cessation of relapse-protocol-therapy (Table 4).

3.4. Comparison of subgroups

The distribution of treatment versus disease-related deaths was significantly different between subgroups ($p = 0.008$) (Table 4): 20% of the 49 patients in group C, who did not survive, died a treatment-related death, whereas all patients in the non-curative groups died of leukaemia. The probability of survival correlated with treatment-intensity after NR ($p < 0.001$, Fig. 1a). One-year-survival rates were not significantly different between subgroups.

To evaluate the impact of SCT on survival, all patients who died during median time from cessation of relapse-treatment to SCT (60 d) and the four group-S-patients, who survived this timeframe, were excluded from further analysis. Median survival was slightly higher in group C ($n = 44/51$; 127 d) than in group P ($n = 15/23$; 110 d). It was also comparable between group-C-patients, who received chemotherapy only ($n = 22/51$; 103 d) and group P. The probability of survival was the highest ($p = 0.001$) for SCT-patients (Fig. 1b).

3.5. Prognostic factors

In multivariate Cox-regression analysis, time-point of relapse and treatment approach after NR proved to be independent predictors of survival duration.

3.6. Factors determining quality of life after NR

3.6.1. Treatment-tolerance

The documented treatment-tolerance was retrospectively categorised as “good”, “medium” or “bad”. About half (56%) of group-C-patients qualified it as “bad”, while 82% in group

Table 3 – Frequencies of efficacy of treatment after non-response (NR) to protocol therapy according to trials ALL-REZ BFM 90[7,8], 95/96[11] and ALL-REZ BFM pilot protocols[14–16] in children and adolescents with first relapse of ALL by treatment approach after NR.

Efficacy of treatment after NR	Treatment after NR						
	Frequencies among subgroups						
	Total of documented cases	Documented patients without antileukaemic approach (group S)	Documented cases with palliative approach (group P)	Documented cases with curative approach (group C)			p
				Chemo only	SCT	Total	
Parameters of efficacy	93 (100%)	19 (100%)	23 (100%)	29 (57%)	22 (43%)	51 (100%)	
Progressive disease	62 (67%)	19 (100%)	17 (74%)	20 (69%)	6 (27%)	26 (51%)	<0.001*
Minor response (BM3)	2 (2%)	–	–	2 (7%)	–	2 (4%)	
Partial remission (BM2)	5 (5%)	–	–	3 (10%)	2 (9%)	5 (10%)	
2ndCR	16 (17%)	–	–	3 (10%)	13 (59%)	16 (31%)	

BM2: partial remission (<25% blasts in an otherwise regenerative bone marrow (BM)).
BM3: minor response (⩾25% BM-blasts); CR: complete remission.
* Group S versus P versus C.

Table 4 – Frequencies of events, survival and frequencies of factors affecting the quality of life of children and adolescents with first relapse of ALL and non-response (NR) to protocol therapy according to trials ALL-REZ BFM 90[7,8], 95/96[11] and ALL-REZ BFM pilot protocols[14–16] by treatment approach after NR.

Parameters after NR	Treatment after NR Frequencies among subgroups				
	Total of documented cases	Documented patients without antileukaemic approach (group S)	Documented cases with palliative approach (group P)	Documented cases with curative approach (group C)	*p*
Events	93 (100%)	19 (100%)	23 (100%)	51 (100%)	
CCR	2 (2%)	–	–	2 (4%)	0.008*
Treatment-related death	10 (11%)	–	–	10 (20%)	
Disease-related death	81 (87%)	19 (100%)	23 (100%)	39 (76%)	
Median survival [d] (minimum; maximum) after cessation of relapse-protocol-therapy		42 (17; 81)	89 (28; 408)**	121 (33; 1856)***	
Factors potentially affecting quality of life					
Location of end-of-life-care	85 (91%)	19 (100%)	21 (91%)	45 (88%)	0.014
Passed away at home	34 (40%)	13 (68%)	7 (33%)	14 (31%)	
Passed away in the hospital	51 (60%)	6 (31%)	14 (67%)	31 (69%)	
Missing values	8 (9%)	–	2 (9%)	6 (11%)	
Subjective tolerance of palliative or curative treatment	27 (29%)	–	11 (48%)	16 (31%)	0.013
"good"	13 (48%)	–	9 (82%)	4 (25%)	
"medium"	3 (11%)	–	–	3 (19%)	
"bad"	11 (41%)	–	2 (18%)	9 (56%)	
Missing values	66 (71%)	–	–	35 (67%)	

CCR: continuous complete remission.
* Treatment versus disease related death.
** One case not documented.
*** Two cases not documented.

P experienced "good" tolerance. This difference was significant ($p = 0.013$) (Table 4).

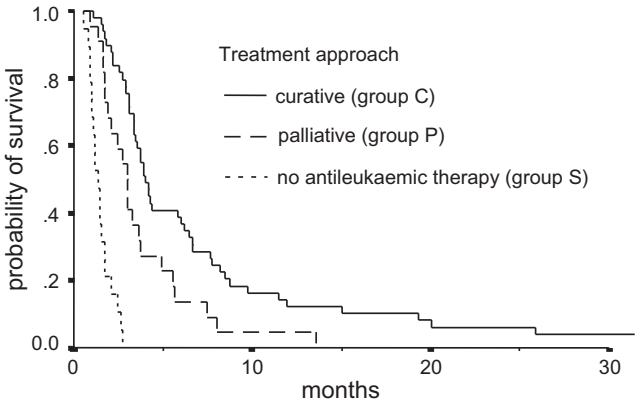

Fig. 1a – Survival probability for children with first relapse of ALL and non-response (NR) to relapse-protocol-therapy according to trials ALL-REZ BFM 90[7,8], 95/96[11] and ALL-REZ BFM pilot protocols[14–16] by treatment approach after NR.

3.6.2. Location of end-of-life care period

Most patients of groups C (69%) and P (67%) died in hospital, most of group S (68%) at home. This difference was significant ($p = 0.014$) (Table 4).

4. Discussion

We here present management and outcome of children with first ALL-relapse and NR to treatment according to ALL-REZ BFM trials[7,8,11] and BFM pilot protocols.[14–16] A substantial, population-based cohort of 93 patients was retrospectively subdivided based on the intensity of treatment given after NR.

The data revealed that most children with NR (55%) received treatment with curative intention and that this approach was not successful. No significant difference in the distribution of relapse-protocols over the treatment approaches chosen after NR was found, implying that NR-management was not determined by the preceding protocol. The time-point of cessation of relapse-treatment due to NR was variable among subgroups, significantly dependent on both relapse-protocol and strategy-group but not associated with subsequent NR-management. The distribution of established risk-factors was inhomogeneous between subgroups. Latter observation might not be random but rather reflects

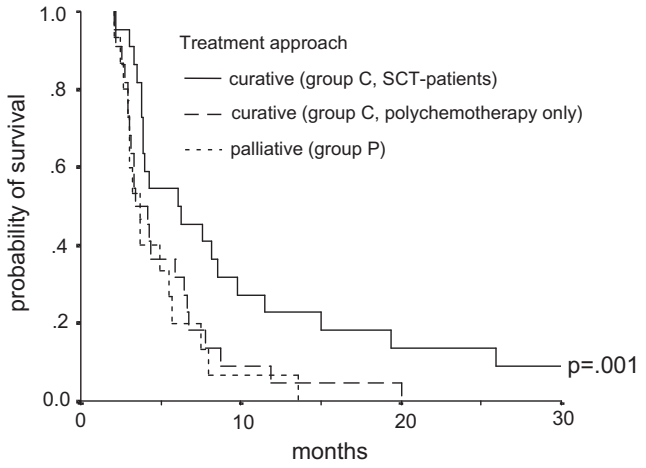

Fig. 1b – Survival probability for children with first relapse of ALL and non-response (NR) to relapse-protocol-therapy (ALL-REZ BFM 90[7,8], 95/96[11], ALL-REZ BFM-pilot-protocols[14–16]), who survived median time to SCT. The censored end of follow-up of two patients still alive is not included.

the assumed prognosis at NR: most patients with HR at first relapse were palliated after NR and, therefore, assigned to groups P or S, respectively, while most children with intermediate-risk at first relapse received further treatment with curative intention after NR (group C).

For most patients, none of the NR-treatment approaches resulted in longterm survival. Partial responses to chemotherapy were observed, most certainly as a consequence of a remaining sensitivity of leukaemia cells to antineoplastic agents. These data might be incomplete, since considerably less diagnostics were performed in group P than in group C (data not shown) and thus minor responses to palliative chemotherapy might have been missed. Nevertheless, all patients in the non-curative groups died of leukaemia after persisting NR, most of them earlier than 1 year after diagnosis of NR. Survival times were longest for group-C-patients who underwent SCT but only two of these are long-term survivors. This small number does not allow any conclusion regarding the efficacy of SCT for patients with NR as indicated previously.[21]

A 2ndCR was obtained in only one third of children treated with curative intention, in 81% of them only after SCT. Most SCT were from MFD. This might reflect both donor-availability and lower treatment-risk compared to alternative donors in an otherwise hopeless situation. Median time from cessation of relapse treatment to SCT was considerably shorter when compared to ALL-REZ BFM[7,8,11] and other trials[22–24] (60 versus 125–155 d). This difference reflects the fact that latter patients received SCT in 2ndCR, while 86% of SCTs reported herein were performed without previous achievement of 2ndCR.

Although, NR to protocol-therapy in patients with ALL relapse can generally be considered as a palliative situation, the majority of patients in this study was treated with curative intention and a substantial number of them died of treatment-toxicity and in hospital. This observation was reported earlier for the management of children in the terminal phase of a lethal disease[25,26] and should reinforce that in palliative situations and times of continuously decreasing resources in health care, the economical aspect of intensive treatment with hospitalisation and the resulting physical and emotional burden for these children and their families need have to be taken into account. Overall, current NR-management has been highly heterogeneous customised and with no discernable difference in outcome between subgroups. The higher median survival rate in group C may be at least in part related to a more favourable risk profile of this cohort. Therefore, it would be inappropriate to generally expect an individual benefit for patients with NR from approaches with curative intent. Furthermore, this study confirms previous reports[27] showing that allogeneic SCT in patients without 2ndCR is ineffective.

With the various treatment approaches analysed in this study, children with relapsed ALL and NR to protocol-therapy have no realistic chance of cure. Therefore, they should be eligible for innovative, ethically approved phase I/II trials. These may provide benefits from new agents with mechanisms of action that have not been applied previously and thus may circumvent treatment resistance of leukaemia cells. If a substantial response can be achieved with a new agent, phase I/II trials should continue with the effective drug. This might finally make allogeneic SCT for patients in 2ndCR and thus reentry to a curative approach is feasible. Several licences have been achieved for this indication in the last years indicating that successful drug development is possible for children with relapsed refractory ALL.[28,29] Therefore, and since this study shows that uncontrolled intensive treatment is not indicated, children with NR to ALL-relapse-protocol-therapy might benefit from a general increase in recruitments to paediatric phase I/II trials. However, with the same dedication, professional palliative care has to be provided and the individual needs of all patients and their families have to be respected.

Conflict of interest statement

None declared.

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Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.09.020.

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