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ORIGINAL ARTICLE

Outcome of poor response paediatric AML using early SCT

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Abstract

Background: Children with poor response acute myeloid leukaemia (AML) generally have a very poor outcome. Allogeneic stem cell transplantation (SCT) is often recommended for these children but the benefit is unclear. The aim of this study was to investigate survival for poor response AML patients treated with SCT. *Material and Methods:* Treatment was given according to the NOPHO-AML 2004 protocol. All patients received AIET (Cytarabine, Idarubicin, Etoposide, Thioguanine) and AM (Cytarabine, Mitoxantrone) as induction. We included poor response defined as > 15% blasts on day 15 after AIET (n = 17) or > 5% blasts after AM (n = 14, refractory disease). Poor response patients received intensively timed induction and proceeded to SCT when a donor was available. *Results:* Thirty-one of 267 evaluable patients (12%) had a poor response. SCT was performed in 25; using matched unrelated donors in 13, matched sibling donors in 6, cord blood donor in 4, and haploidentical donor in two. The median follow-up for the 31 poor responding patients was 2.6 years (range 0.4 – 8.1 years) and 3-year probability of survival 70% (95% CI 59-77%). *Conclusions:* The poor responders in the NOPHO-AML 2004 protocol had a favourable prognosis treated with time-intensive induction followed by SCT.

Key words acute myeloid leukaemia; early stem cell transplantation; survival; poor response

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The role of stem cell transplantation (SCT) in the treatment of acute myeloid leukaemia (AML) in children is controversial. There is consensus not to advocate autologous (auto) SCT as most studies show no benefit of auto-SCT compared with chemotherapy alone. However, the possible benefit of allogeneic SCT (SCT) is unclear. Some studies have found a benefit of SCT compared with chemotherapy alone, while others have found no significant difference between the two treatments or only improvement in subgroups of AML (1, 2). However, methodological difficulties complicate interpretation of results and, in particular, comparability of results between the different AML trials may be problematic. In Europe, many investigators prefer chemotherapy alone in the treatment of paediatric AML in first complete remission (CR1) and recommend SCT only to patients who have a poor prognosis genetic aberrations or in second CR (2).

However, the definition of the patients with a poor prognosis is not consistent throughout the different AML treatment protocols. Most investigators agree that specific genetic aberrations, such as *FLT3*-ITD (3) and monosomy 7 (4), and high blast count after initial treatment (2, 5, 6)

predict a poor prognosis but the exact definition vary among the trials.

Recent data also demonstrate the important prognostic role of minimal residual disease (MRD) in patients with AML (7–11).

The NOPHO-AML 2004 protocol introduced a definition of poor response based upon evaluation after the first and second induction course. The poor responders were treated time intensively and allocated to SCT with the best available donor. Here, we report the results of the time-intensive therapy and early SCT in children with AML and poor response to the first induction or with refractory disease.

Patients and methods

Eligibility

Since 1984, all children in the Nordic countries under the age of 15 yr and diagnosed with AML have been treated according to the NOPHO-AML protocols. Some centres have included children up to the age of 18 yr. Since late 2007 also patients from Hong Kong have been included.

Here, we report on patients diagnosed between 1 January 2004 and 31 December 2011 and treated according to the NOPHO-AML 2004 protocol (12). The patients were followed until March 2012. Informed consent and ethical approval were obtained according to national regulations.

Diagnosis

The diagnosis and therapy was centralised to the 23 University Hospitals in the five Nordic countries and Hong Kong. SCT was performed in eight transplant centres. Diagnosis was achieved by morphologic analysis of bone marrow aspirates according to FAB and WHO classifications (13, 14). Patients with Down syndrome and promyelocytic leukaemia were not included.

Treatment

The protocol included two anthracycline and low-dose cytarabine-based induction courses followed by four high-dose cytarabine-based consolidation courses. Treatment has recently been described in details by Abrahamsson *et al.* (12) and will only be presented in short here. The induction treatment consisted of AIET: cytarabine 200 mg/m^2 continuous infusion day 1–4; idarubicin 12 mg/m^2 day 2, 4 and 6; etoposide 100 mg/m^2 continuous infusion day 1–4; and 6-thioguanine 100 mg/m^2 bid orally day 1–4; and AM: cytarabine 100 mg/m^2 continuous infusion day 1–5 and mitoxantrone 10 mg/m^2 day 1–3. Patients with >5% blasts day 15 after AIET were recommended to start AM immediately, whereas those with <5% blasts were allowed time for hematologic recovery before AM. Children not in remission after AIET and AM (refractory disease) proceeded to FLAG (fludarabine, cytarabine, granulocyte colony-stimulating factor). The treatment outline is illustrated in Fig. 1(15).

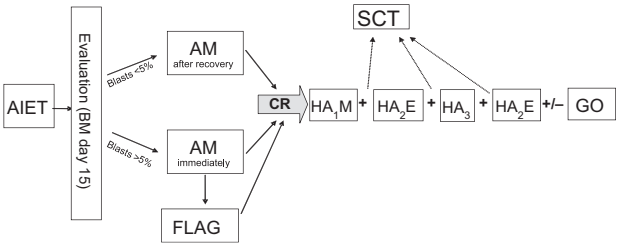

Figure 1 Treatment outline for the NOPHO-AML 2004 protocol. Poor responders were scheduled for allo-SCT after the first and before the last consolidation course. SCT was not recommended for non-poor-responding patients. The figure is adapted from Hasle *et al.* (15).

HLA typing of the patient and family was recommended to be performed at diagnosis for all patients. Patients with poor response to induction treatment were eligible for SCT as consolidation. Matched sibling donors (MSD), matched (9/10 or 10/10) unrelated donors (MUD) or cord blood donors (CBD) were accepted. In cases where matched donors were not available, HLA-mismatched and haploidentical donors were accepted at the discretion of the treating clinicians. Poor responders were scheduled for SCT after the first and before the last consolidation course. SCT was encouraged to be performed after a total of three courses. Conditioning regimens before SCT and graft versus host disease (GvHD) prophylaxis were according to local guidelines and varied. Conditioning regimen was myeloablative in all patients and consisted of various combinations of busulfan (Bu), cyclophosphamide (Cy), melphalan (Mel), fludarabine (Flu) and total body irradiation (TBI).

MRD monitoring

Minimal residual disease monitoring was performed prior to SCT when possible. Leukaemia-associated immunophenotypes (LAIP) were identified in bone marrow specimens at diagnosis and pre-SCT by flow cytometry with a detection limit around 10^{-4}. Fusion genes and *WT1* gene expression were detected by quantitative RT-PCR as previously described by Ommen *et al.* (16).

Definitions

Early response was evaluated day 15 post-AIET. Patients with more than 5% blasts were treated immediately, whereas patients with good response had repeat bone marrow examinations performed following hematologic regeneration, and CR was assessed according to international recommendations (17, 18).

Resistant (refractory) disease was defined as no CR after two induction courses.

Patients were classified as good responders, if they were in CR after first induction course with AIET or if they had 5–15% blasts after AIET but achieved remission after the second induction course. Patients were considered as poor responders if they had more than 15% blasts on day 15 after AIET and/or achieved no CR after AM. Blast count was based on morphologic assessments of bone marrow smears and confirmed by flow cytometry. Patients with favourable cytogenetics, defined as t(8;21)(q22;q22), inv(16)(p13;q22) and t(9;11)(p21;q23), were not candidates for SCT in CR1 if they achieved CR after AM regardless of the day 15 response (12).

Statistical analysis

Probability of overall survival (OS) was calculated from time of diagnosis to death of any cause. Probability of event free survival (EFS) was calculated from time of diagnosis to the last date the patient was known to be alive without an event. Relapse, second malignancy, resistant disease and death were considered as events. Probability of relapse free survival (RFS) was calculated from time of diagnosis to the time of relapse or the last date the patient was known to be alive without a relapse (death during induction or in complete remission and second malignancy were censored at the time of the event). Probability of disease free survival (DFS) was calculated from time of SCT to the last date the patient was known to be alive. Relapse, second malignancy, and death was considered as events.

The median follow-up times were calculated for those alive. SPSS (IBM, New York, NY, USA) Statistics Data Editor 18 software was used for the statistical analysis. Differences in subgroups were calculated using the Pearson's chi-squared test. The Kaplan–Meier method was used to estimate OS, EFS, RFS and DFS. Differences in subgroups were assessed using the log-rank test. Data are analysed according to the intention to treat principle (ITT).

Results

Patient characteristics and overall outcome

A total of 274 patients were treated according to the NOPHO-AML 2004 protocol. Seven patients died during the first 15 d of induction treatment and were excluded as evaluation for treatment response was not possible. The characteristics of the 267 patients are summarised in Table 1. The male/female ratio was 1.3, and the median age at diagnosis was 6.0 yr (range, 0–17 yr). The median white blood cell count (WBC) at presentation was 20.8×10^9 /L (range, $0.6–427 \times 10^9$ /L). Favourable cytogenetics was found in 98 patients (37%), 31 patients (12%) had 11q23 other than t(9;11) and 58 (22%) had normal karyotype. The median follow-up for all of the 267 patients alive was 3 yr (range, 0.17–8.12) and the estimated 5-yr OS 72% (SE 3).

Table 1 Characteristics of the 267 patients with evaluable day 15 response

Characteristics	Good response[1] *N* (%)	Poor response[2] *N* (%)	*P*- value
Sex			
Male	130 (55)	19 (61)	0.57
Female	106 (45)	12 (39)	
Age			
0–1 yr	61 (26)	3 (10)	0.11
2–9 yr	92 (39)	13 (42)	
10 + yr	83 (35)	15 (48)	
Median age	6.0	9.0	
White blood count			
$0–9.9 \times 10^9$ /L	83 (35)	12 (39)	0.43
$10–100 \times 10^9$ /L	121 (51)	10 (32)	
$>100 \times 10^9$ /L	32 (14)	9 (29)	
Median	19.8	30.5	
FAB classification			
M0	15 (6)	3 (10)	0.09
M1	27 (11)	4 (13)	
M2	61 (26)	5 (16)	
M4	41 (17)	5 (16)	
M5	56 (24)	4 (13)	
M6	4 (2)	0 (0)	
M7	19 (8)	2 (6)	
Other/unclassified	13 (6)	8 (26)	
CNS disease			
Yes	22 (9)	4 (13)	0.83
No	210 (89)	27 (87)	
Data missing	4 (2)	0 (0)	
Cytogenetics			
t(8;21)	43 (18)	0 (0)	0.00
inv(16)	26 (11)	0 (0)	0.05
t(9;11)	29 (12.5)	0 (0)	0.03
11q23 non t(9;11)	27 (11.5)	5 (16)	0.77
Other abnormalities	66 (28)	13 (42)[3]	1.00
Normal karyotype	45 (19)	13 (42)	0.01
FLT3			
FLT3-ITD	14 (6)	3 (10)	0.21
Wild type	141 (60)	15 (48)	
Not tested	69 (29)	13 (42)	
ALM (D835/I836)	12 (5)	0 (0)	
SCT			
Yes	15 (6)	25 (77)	0.00
No	221 (94)	6 (23)	
Outcome			
3-yr EFS	54%	26%	
3-yr RFS	58%	66%	
3-yr OS	74%	70%	

[1]Good response ($N = 236$): <5% after AIET or 5–15% blasts after AIET and <5% after AM.
[2]Poor response ($N = 31$): >15% after AIET and/or >5% after AM.
[3]Including monosomy 7 in three, del(7q) in two, and trisomy 8 in two patients.

Response to induction treatment

Thirty-one of 267 patients (11.6%) had a poor response after induction treatment. A flow chart of the response to therapy is presented in Fig. 2.

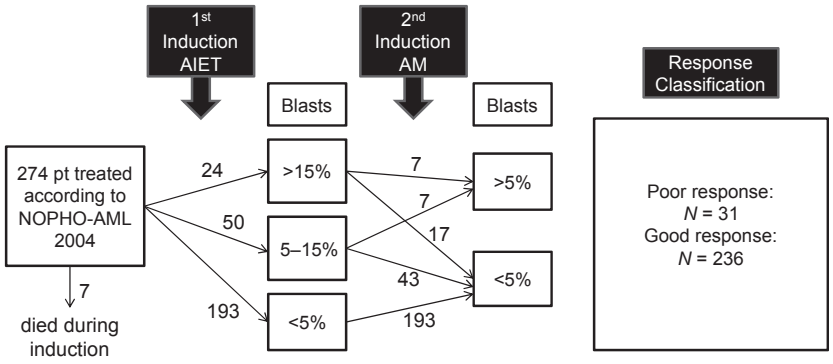

Figure 2 Flow diagram of patient responses. Seven patients died during induction and were excluded as evaluation of their responses was not possible. Eleven of 14 with >5% blasts after AM proceeded to FLAG and nine of these achieved remission subsequently. Poor response ($N = 31$): >15% after AIET or no remission after AM and no favourable cytogenetics. Good response ($N = 236$): blasts <15% after AIET and remission after AM.

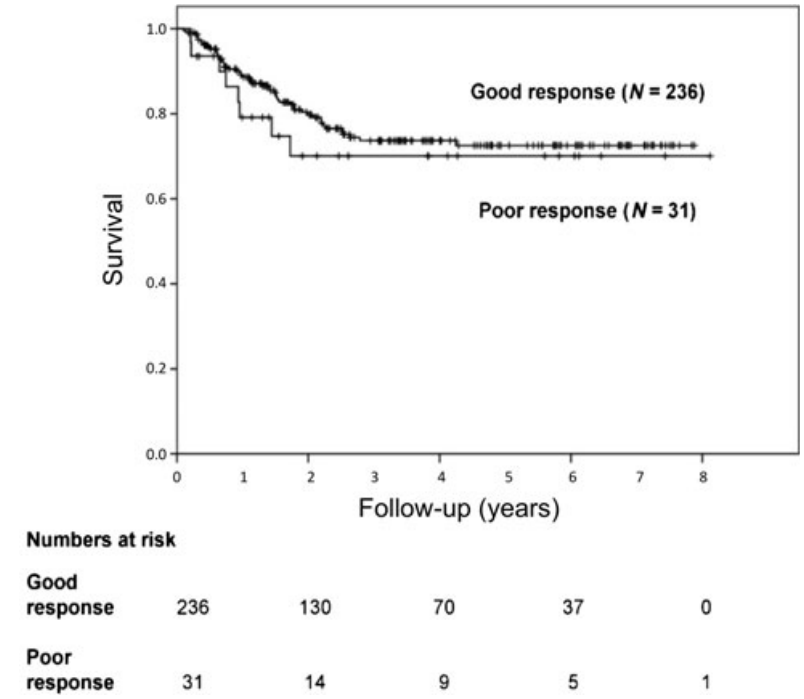

Figure 3 Overall survival (OS) for good responders ($N = 236$) and poor responders ($N = 31$) in NOPHO-AML 2004. The 3-yr OS for good responders and poor responders was 73.7% (SE 3.3) and 70.1% (95% confidence interval 59 –77%) ($P = 0.47$), respectively.

Twenty-four patients had more than 15% blasts after AIET, and seven patients had less than 15% blasts but did not achieve CR after AM.

The median time from start of AIET to start of AM was only 21 d (range, 13–47 d) for the poor responders compared to 32 d (range, 15–141 d) for the good responders.

Characteristics and outcome of poor responders

There was no significant difference between the poor responders and the good responders in terms of sex, age, WBC at diagnosis and CNS disease. None of the poor responders had favourable cytogenetics at diagnosis, but 13/31 had normal karyotype (Table 1). *FLT3*-ITD was found in three of 18 poor responders tested vs. 14 of 167 tested in the total cohort (3).

The median follow-up time for the 31 poor-responding patients was 2.6 yr (range, 0.4–8.1 yr), and the 3-yr OS was 70% (95% confidence interval 59–77%), Fig. 3. The EFS was only 26% (95% confidence interval 18–33%) due to inclusion of patients with refractory disease ($N = 14$). The RFS was 66% (95% confidence interval 57–73%).

In total, 25 poor responders received SCT (Table 2). Thirteen (52%) of 25 achieved remission after two courses, nine (36%) after three and three (12%) did not achieve remission

Table 2 Characteristics of poor-responding patients (n = 25) undergoing SCT

Characteristics	*N*
Response	
>15% after AIET and >5% after AM	5
>15% after AIET and <5% after AM	13
5–15% after AIET and >5% after AM	7
Courses before SCT	
AIET + AM	1
AIET + AM + FLAG	9
AIET + AM + FLAG + HA_1M	1
AIET + AM + FLAG × 2 + HA_2E_1 + HA_3	1
AIET + AM + HA_1M	7
AIET + AM + HA_1M + HA_2E	4
AIET + AM + HA_1M + HA_2E + HA_3	1
AIET + AM + HA_1M + HA_2E_1 + HA_3 + HA_2E_2	1
% Blasts by morphology at SCT	
>15%	2
5–15%	1
<5%	22
MRD before SCT	
>1%	7
0.1–1%	4
0.01–0.1%	4
<0.01%	1
Missing/not done/non-evaluable	9
Interval from diagnosis to SCT	
<3 month	2
3–6 months	17
>6 months	6
Median interval in months	4.8
Donor type	
Matched unrelated donor[1]	12
Matched sibling donor	6
Cord blood donor	5
Haploidentical paternal donor	2
Stem cell source	
Peripheral blood	5
Bone marrow	15
Cord blood	5
Conditioning regimen	
BuCyMel	9
BuCy	9
TBI Cy	1
Other[2]	6

HA, High-dose Cytarabine; M, Mitoxantrone; E, Etoposide; Bu, Busulfan; Cy, Cyclophosphamide; TBI, total body irradiation; Mel, Melphalan.

[1]One patient with HLA-match 8/10.

[2]Fludarabine based in four patients and Bu+Mel based in one patient. One received Clofarabine, Thiotepa and Melphalan.

after induction. The median time from diagnosis to transplantation was 143 d (range, 81–259 d), and a median of three courses (range 2–6) was given before SCT. The donors were MUD (48%), MSD (24%), CBD (20%) or haploidentical donor (8%). One patient received MUD with 8/10 match, all other MUD had 9/10 or 10/10 matches. Time from diagnosis to transplantation was for MUD 4.8 months, for MSD 3.2 months and for CBD 5.5 months. The conditioning regimen was based on Bu in 19 (76%) (BuCy in 9, BuCyMel in 9 and BuMel in 1), TBI in one (4%) and Flu in four (16%) patients. Clofarabine, thiotepa and Mel were used in one patient (4%).

The median follow-up for the poor responders receiving SCT (N = 25) was 3.8 yr (range, 0.4–8.1 yr), and the 3-yr OS was 78% (95% confidence interval 70–87%). Probability of DFS from time of SCT for the 25 patients was 74% (95% confidence interval 65–83%). Five patients (20%) died after relapse following SCT. There were no treatment-related deaths (TRD).

Prior to SCT, three patients had morphologic residual disease including two patients with overt disease (more than 40% blasts) who both remained alive in long-term remission.

MRD before SCT was assessed and evaluable in 16 of 25 patients. Most patients had MRD assessed by flow cytometry (14/16). Nine of eleven patients with MRD levels $\geq 0.1\%$ and four of five patients with MRD $\leq 0.1\%$ blasts are alive and in remission. Three of the patients who relapsed after SCT had MRD levels of 10%, 1.1% and 0.03% at SCT. The last three patients who relapsed after SCT did not have MRD measured but had <5% blasts based on morphology.

Acute GvHD occurred in 16 of 25 patients; grade 1 in seven, grade 2 in two, grade 3 in six, grade 4 in one. Chronic GvHD was reported in 10 of 25 patients; limited in seven and extensive in three patients.

Six of 31 poor responders did not receive SCT. Three of these died of progressive disease before SCT could be performed, two relapsed before SCT and were transplanted in second CR (both were alive at last follow-up), and no eligible donor was available for the last patient who relapsed 1 yr after diagnosis.

Outcome of good responders

The median follow-up for the good responders was 3 yr (range, 0.0–7.9 yr). The 5-yr OS and EFS were 73% (SE 3) (Fig. 3) and 52% (SE 4), respectively. Seven patients died in CR, 85 relapsed (of these 44 patients died) and two experienced a second malignancy.

Discussion

We report outcome for paediatric AML patients with a poor response to initial therapy and treated according to the NOPHO-AML 2004 trial. A previous study from Abrahamson *et al.* has presented results from the NOPHO-AML 2004 trial (12). However, the present study focuses on patients with poor response. We include more patients with poor response, more details about response, therapy and conditioning regimens, and a longer follow-up than the study from Abrahamsson *et al.* The previous NOPHO-AML 93 trial found that the

patients with a poor response to initial therapy and treated with SCT only if a MSD was available had a very poor outcome (OS 44%) (5). In the NOPHO-AML 2004 protocol, patients with poor response were treated more intensively with a short interval between the two induction courses with median 21 d vs. 32 d in the good responder group (12). Only sibling donors were recommended in the NOPHO-AML 93 trial in contrast to the best available donor for all poor responders in NOPHO-AML 2004. HLA typing was recommended at time of diagnosis and succeeded in identifying a donor in 30/31 from this mainly (77%) Caucasian population and allowed us to perform SCT early (median time = 4.8 months).

The aggressive induction approach and consolidation were successful resulting in complete remission after the second course of chemotherapy in half of the poor responders and before SCT in 22/25. The subsequent SCT was well tolerated without any TRD and relapse in only 6/25.

The burden of the long-term effects of SCT was limited as only three of the patients had extensive cGvHD.

Our results showed a very low EFS and a large difference between EFS and OS for poor-responding patients. Fourteen of the poor-responding patients had refractory disease as they did not achieve remission after two induction courses and by definition had event day zero and an EFS of zero.

Most of our patients were treated with a MUD (12 of 25) compared with MSD in the previous protocol, and the good outcome in the present study may in part be due to the early SCT and also the benefit of a graft vs. leukaemia (GvL) effect. Accordingly, recent trials have presented favourable outcome of MUD transplant in children (19–22) in contrast to previous studies (23–25). The improved results in MUD SCT may be due to better supportive care and donor selection by genomic typing technology, and MUD seems now to be an equivalent alternative to MSD in the treatment of paediatric patients with AML.

Conditioning regimens varied according to local guidelines. The low number of patients did not allow a comparison of the different conditioning regimens. However, most of the patients had received regimens based on BuCy and BuCyMel, which are known to have a powerful myeloablative effect and may have contributed to the good survival. BuCyMel was introduced by Locatelli *et al.* (26, 27) and found to be an effective preparative regimen especially used in juvenile myelomonocytic leukaemia and myelodysplastic syndrome.

In general, patients with refractory disease have a very dismal prognosis (28, 29), and SCT seems to be the only therapy with a curative potential. This was suggested in a study of children with AML and monosomy 7 where patients with refractory disease treated with SCT (N = 17) had an OS of 31%, while all non-SCT-treated refractory patients (N = 58) died within 17 months (4).

Three patients in the present trial had persistent disease based on morphology when receiving SCT. One died of progressive disease less than a year after SCT and two with approximately 40% blasts at SCT are still alive in remission with a median follow-up of 45 months.

Table 3 Survival of poor responders in six paediatric AML trials

Trials	Definition of poor responders	N	% poor responders in the protocols	Survival ITT
NOPHO-AML 93 (5)	>5% on day 15	57	23	5-yr OS: 44%
NOPHO-AML 2004 (present study)	>15% blasts on day 15 or 5–15% blasts on day 15 and/or >5% after second induction course	31	12	3-yr OS: 70%
BFM-AML 98 (30)	>5% on day 15, or other high-risk criteria	281	59	5-yr OS: 54%
MRC-AML 12 (31)	>15% blasts on day 15	93	16	10-yr OS: 39%
CCG 213 (32)	>15% blasts on day 14	180	36	7-yr OS: 27%
AML02 (7)	>25% blasts after initial course or persistent MRD after three courses	79	34	3-yr OS: 55%

MRD prior to SCT was assessed when possible; however, data were too sparse to make any statistical conclusions. Nonetheless, nine of eleven patients with MRD higher than 0.1% remain alive without disease, indicating that also in the present study, SCT is effective in AML with significant levels of residual disease.

The favourable outcome of the NOPHO-AML 2004 trial seems to exceed results presented earlier for patients with high blast count in the bone marrow after initial treatment (Table 3). The Berlin-Frankfurt-Münster-98 trial (BFM-AML 98) found a survival of 55% (30); the Medical Research Council 12 trial (MRC-AML 12) a survival of 39% (31); the Children's Cancer Group trial (CCG 213) a survival of 27% (32); and in the recent AML02 trial a survival of 55% (7). Finally, a large study by Horan *et al.* with patients from COG and MRC found a survival of only 33% in high-risk patients defined by poor response or cytogenetics (33).

The potential superior outcome in the present study may have many reasons, especially, since several protocol components differ between our trial and those mentioned above.

Regarding the protocol, the most important differences, may be the short time interval between first and second induction course and treatment with early SCT with the best available donor in NOPHO-AML 2004. The BFM-AML 98 trial, the MRC-AML 12 trial, NOPHO-AML 93 and the CCG 213 trial, offered SCT only if a MSD was available (5, 30–32).

In contrast to our findings, the BFM-AML 98 trial, the MRC-AML 12 trial and the AML02 trial found no benefit

of SCT compared with chemotherapy in the poor-responding group (7, 30, 31). AML02, however, found a benefit when limiting analysis for high-risk patients with MRD above 1% after induction 1.

The study by Horan *et al.* also concluded that high-risk AML did not benefit from SCT (33). However, the total number of high-risk patients treated with SCT was only nine and too low for a conclusion of SCT in high-risk AML.

As stated in the introduction, a comparison between different studies may be problematic.

Furthermore, our study was limited by the small number of patients, which made the differences in survival between the present study and the studies above non-significant.

The potential superior outcome in the present study could be that the treatment strategy in the NOPHO-AML 2004 protocol was superior. It could, however, also be that the patients in our study simply had a better prognosis than the patients in the studies above. Nonetheless, 11 of our patients were MRD positive at SCT, which strongly indicates a poor prognosis.

Most of the studies mentioned above do not specifically look at poor-responding patients who eventually achieve remission as for most of the patients in our study, which may also influence the results.

We included all poor-responding patients regardless of their disease state at SCT, however, we managed to bring almost all patients in morphologic remission by SCT, and the survival was very good with very few relapses and no TRD.

Over the past few years, SCT procedures have improved and are associated with lower treatment-related mortality now than before. Genomic typing, availability of unrelated donors and supportive care including better virus surveillance have also improved over the past few years and made SCT a better option in the treatment of paediatric AML.

The strategy in our study, with SCT being an important component of treatment, resulted in a 3-yr survival of 78% and indicates a benefit of SCT for patients with a poor response in the NOPHO-AML 2004 protocol.

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Conflict of interest

None.

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