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ORIGINAL REPORT

Pathways Through Relapses and Deaths of Children With Acute Lymphoblastic Leukemia: Role of Allogeneic Stem-Cell Transplantation in Nordic Data

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ABSTRACT

Purpose
Our focus was on patients with pediatric acute lymphoblastic leukemia (ALL) who experienced relapse or died without becoming transplantation candidates. The purpose was to outline measures needed to improve the outcome.

Patients and Methods
We analyzed our population-based 20-year data on 3,385 Nordic children with ALL treated on Nordic Society for Pediatric Hematology and Oncology ALL protocols, and described the flow of these patients through relapses, remissions, and deaths as a result of toxicity, demonstrating where major patient losses occurred.

Results
In total, 854 patients (25%) had a first and 274 patients (8%) had a second ALL relapse. *P* for survival after the first relapse was .35 ± .02. The induction mortality (2.2%, primary; 10.3%, first relapse; 26.3%, second relapse) and remission mortality (1%, first complete remission [1CR]; 19%, second CR [2CR]) were significant; transplantation-related mortality (TRM) only represented 15% (69 of 459) of the deaths as a result of toxicity. Of the 766 patients entering 2CR, 29% underwent transplantation (*P* for survival, .46 ± .04), whereas 71% continued receiving chemotherapy (*P* for survival, .39 ± .02). Children with stem-cell transplantation indications in 2CR, if they did not undergo transplantation, generally died or had a second relapse. The patient groups that underwent transplantation in 1CR (n = 84), 2CR (n = 220), and ≥ 3CR (n = 62) represented different risk profiles. Those with allogeneic stem-cell transplantation (allo-SCT) in ≥ 3CR (*P* for survival, .37 ± .07) had an ALL and first relapse with favorable features.

Conclusion
Major patient losses occurred through mortality as a result of toxicity and resistant disease during the pathways before allo-SCT. After relapse, more patients were lost to mortality as a result of toxicity during conventional chemotherapy compared with TRM. After second relapse, the chance for rescue by allo-SCT in ≥ 3CR was minimal. The question of whether transplantation is recommended after ALL relapse should be carefully addressed, and more efficient relapse protocols should be launched.

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INTRODUCTION

Currently, approximately 80% of pediatric acute lymphoblastic leukemia (ALL) can be cured.[1-5] However, emphasis needs to be put on the 20% who still have a poor outcome. The therapy of choice for many patients with recurrent ALL is allogeneic stem-cell transplantation (allo-SCT), in which major developments have been made. In pediatric ALL, allo-SCT has been investigated extensively.[6]

However, rarely, if ever, have patients undergoing transplantation been analyzed against the background of the whole population of pediatric ALL to describe the pathways of the patients selected or not selected for allo-SCT. Randomized studies have been difficult to conduct in evaluating the risks of allo-SCT versus those of conventional chemotherapy.[7] In the Nordic pediatric ALL material, we have achieved survival results that compare favorably in the European context.[3,8] With our 100% population-based data, the extended follow-up allowed us to describe the flow of ALL patients through repeat and late relapses, remissions, and deaths as a result of toxicity to illustrate the role of

Table 1. Key Characteristics of the NOPHO ALL Data (n = 3,385)

Characteristic	Diagnosis in 1981 to 1991		Diagnosis in 1992 to 2001		Total	
	No. of Patients	%	No. of Patients	%	No. of Patients	%
All patients	1,655	100	1,730	100	3,385	100
Sex						
Male	876	53	941	55	1,817	54
Female	779	47	789	45	1,568	46
Age at diagnosis, years						
1 to < 10	1,377	83	1,445	84	2,822	83
≥ 10	278	17	1,730	16	563	17
WBC × 10^9/L						
< 10	828	50	886	51	1,714	51
10 to < 100	669	40	682	39	1,351	40
100 to < 200	85	5	88	5	173	5
≥ 200	73	4	74	4	147	4
Lineage						
Non–T-cell lineage	1,386	84	1,541	89	2,927	87
T-cell lineage	136	8	163	9	299	9
Unknown	133	8	26	2	159	5
CNS leukemia						
Present	61	3	38	2	99	3
Absent	1,588	96	1,690	98	3,278	97
ND	6	< 1	2	< 1	8	—
Risk category						
SR	649	39	602	35	1,251	37
IR	543	33	627	36	1,170	34
HR	463	28	501	29	964	29

Abbreviations: NOPHO, Nordic Society for Pediatric Hematology and Oncology; ALL, acute lymphoblastic leukemia; ND, not defined; SR, standard risk; IR, intermediate risk; HR, high risk.

allo-SCT as a whole. Our aim was to focus on patients who died during the process before allo-SCT, to determine where major patient losses occurred and where the improvements in therapy need to be made.

PATIENTS AND METHODS

Patients

This population-based Nordic data from Denmark, Finland, Iceland, Norway, and Sweden includes 100% of children diagnosed with ALL during 1981 through December 31, 2001 (Table 1). For this analysis we excluded those younger than 1 year (n = 106) and ≥ 15 years of age at diagnosis (n = 86), and B-cell ALL (n = 49).

Bone marrow (BM) relapse was defined morphologically with ≥ 5% blasts in the BM. CNS relapse was diagnosed as ≥ 5 WBC/μL in the CSF with blasts, or with defined neurologic symptoms. Testicular relapse was defined as a painless enlargement verified by biopsy. Two relapse categories, group 1 and group 2, were defined. At the first relapse, group 1 included BM relapses within 36 months of diagnosis. Group 2 included all other relapses (ie, isolated extramedullary relapses and all relapses beyond 36 months after diagnosis). At the second relapse, group 1 included BM relapses, and group 2 included the other relapse types.

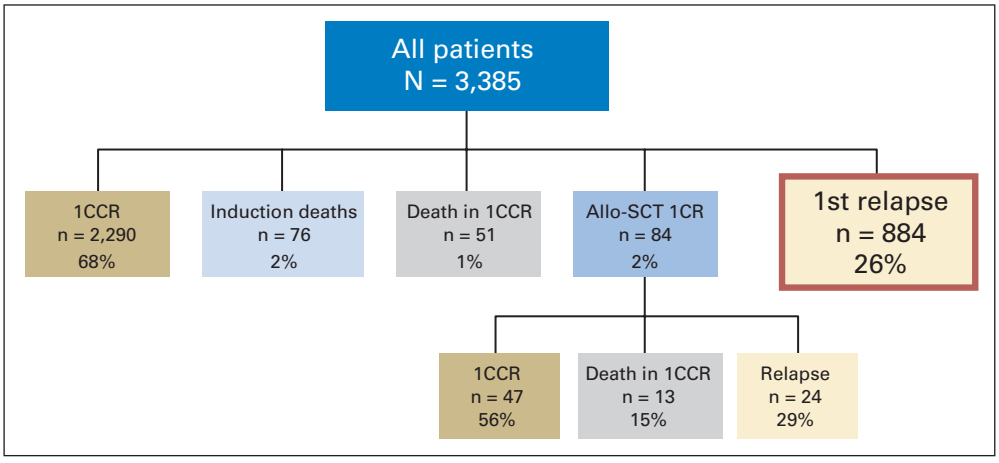

Fig 1. All children with acute lymphoblastic leukemia (ALL) in the population-based Nordic Society for Pediatric Hematology and Oncology (NOPHO) study diagnosed between July 1981 and December 31, 2001. Induction deaths include both resistant disease and deaths as a result of toxicity. Deaths in CCR were toxic complications or infections. 1CCR, continuous complete first remission; Allo-SCT 1CR, patients who underwent allogeneic stem-cell transplantation in first remission due to very high risk ALL.

Table 2. Key Characteristics of Children With ALL Who Underwent Transplantation in ≥ 3CR (n = 62)

Characteristic	No. of Patients
Age at initial diagnosis, years	
Mean	6
Median	5
Range	1-14
Sex	
Male	37
Female	25
Initial risk category	
SR	19
IR	26
HR	17
Immunophenotype	
T cell	4
Precursor B	57
ND	1
Time of first relapse, months	
< 24	13
24 to < 36	19
36 to < 48	16
≥ 48	14
Months from diagnosis	
Median	43
Range	18-97
Receiving therapy (n = 21), months from diagnosis	
Median	24
Range	3-37
Not receiving therapy (n = 42), months from discontinuation of therapy	
Median	14
Range	2-66
Site of first relapse	
BM	33
BM combined	7
CNS	14
Testis	7
Other	1
Category of first relapse*	
Group 1	13
Group 2	49
Indications for allo-SCT in 2CR	
Clear	12
Controversial	34
None	16
Site of second relapse	
BM	32
BM combined	14
CNS	12
Testis	3
Other	1
Category of second relapse	
Group 1	46
Group 2	16
Time from first to second relapse, months	
Median	23
Range	2-91
Site of third relapse (n = 2)	
BM	1
ND	1
Status at allo-SCT	
3CR	60
4CR	2
> 4CR	0
Age at allo-SCT, years	
Mean	11.9
Median	10.9
Time from initial diagnosis to allo-SCT in 3CR, months	
Mean	69
Median	66
Range	9-141
Allogeneic donor	
HLA-identical sibling	24
Parent	3
URD	35
Stem cell grafts used	
BM	56
PBSCs	5
Cord blood	1

Abbreviations: ALL, acute lymphoblastic leukemia; 2CR, second complete remission; 3CR, third complete remission; SR, standard risk; IR, intermediate risk; HR, high risk; ND, not defined; BM, bone marrow; 4CR, fourth complete remission; allo-SCT, allogeneic stem-cell transplantation; URD, unrelated donor; PBSCs, peripheral-blood stem cells.

*Relapse categories: at first relapse, group 1 = BM relapse within 36 months of diagnosis; group 2 = others. At second relapse, group 1 = BM relapse; group 2 = others.

Therapy for ALL

The patients were treated initially according to Nordic ALL protocols.[3,9,10] From July 1981 to June 1986, there was a common protocol for standard-risk (SR) ALL, from July 1986 to December 1991 for both SR and intermediate-risk (IR) ALL, and from January 1992 to December 2001 for three risk categories: SR, IR, and high-risk (HR) ALL. In the earlier era, Berlin-Frankfurt-Münster group (BFM) or BFM-based protocols were used for HR patients.

For ALL relapse, both Nordic HR ALL protocols[10] and BFM ALL relapse protocols[11] were used. Patients with CNS relapses received craniospinal irradiation (24 Gy cranial, 12 Gy spinal), and patients with testicular relapses received 24 Gy to both testicles. High-dose chemotherapy with autologous stem-cell rescue was administered to 49 patients in second complete remission (2CR), who are included in the chemotherapy group in this analysis.

Allo-SCT was performed in children with very HR ALL in first complete remission (1CR), earlier using HLA-identical sibling donors[12] and later also with unrelated donors (URDs).[10] The transplantation indications applied for ALL in 1CR and 2CR, the preparative regimens, and use of graft-versus-host disease (GVHD) prophylaxis have been described.[10,12-14] The patients underwent transplantation at seven Nordic centers.

We focused specifically on the 62 children who underwent transplantation in or beyond third remission (3CR; Table 2). The preparative regimens were without total body irradiation (n = 18) or with total body irradiation (n = 44). GVHD prophylaxis was mostly cyclosporine plus short-course methotrexate. HLA-identical sibling donors were used in 24 transplantations, phenotypically compatible parental donors were used in three transplantations, and URDs were used in 35 transplantations. Of the URDs, 31 were six of six and four were five of six matched. Standard nucleated cell doses and unmanipulated grafts were used.

Statistical Methods

SPSS statistical software (SPSS Inc, Chicago, IL) was used.[15] The events and end points after each relapse and SCT were death as a result of toxicity,

next relapse, or second malignancy (SMN). The overall survival (OS) and event-free survival (EFS) for 1CR, 2CR, and 3CR were calculated by the Kaplan-Meier method.[16] Differences in outcome were compared with the log-rank test.[17] A stepwise multiple regression analysis according to Cox was used to identify prognostic factors. Patient accrual for the entire data set discontinued on January 1, 2002, and accrual for the first relapses discontinued on January 1, 2004. The data were frozen for follow-up at January 1, 2006, allowing a minimum follow-up of 2 years for the patients experiencing relapses. The mean follow-up time for survivors after the first relapse was 17 years for patients diagnosed during 1981 to 1991, and 9 years for those diagnosed during 1992 to 2001.

RESULTS

The majority (68%) of our Nordic ALL patients survive in continuous complete first remission after the original chemotherapy (Fig 1). During the latter time period, the proportion in 1CR increased, whereas the induction deaths and first relapses decreased, and those undergoing allo-SCT in 1CR more than tripled (Fig 2A and 2B).

First ALL Relapse

In total, 884 children (26%) experienced a first malignant event: 854 were ALL relapses and 30 were SMNs (Fig 3A). Median time from diagnosis to first relapse was 28 months (range, 2 to 227 months). The subsequent outcomes of these patients are illustrated in Figure 3A. Of the first ALL relapses, 417 (49%) were group 1 (Fig 3B), and 437 (51%) group 2 relapses. After the first relapse, *P* for 10-year overall survival was .35 ± .02 years.

After the first ALL relapse, 88 patients (10%) died within 3 months. These were deaths as a result of toxicity due to severe infections, often with resistant underlying disease. These 88 patients had over-representation of HR-ALL and T-cell ALL (T-ALL; Table 3) compared with the entire Nordic Society for Pediatric Hematology and Oncology (NOPHO) data (Table 1), with 90% relapsing within 36 months of diagnosis.

ALL in Second Remission

Of the 766 children who achieved 2CR, 220 (29%) underwent allo-SCT in 2CR, and 546 (71%) continued receiving chemotherapy (Fig 3A; Table 3). The relapse risk categories group 1 and group 2 were 52% and 48% in children proceeding to allo-SCT, and 44% and 56% in those continuing on chemotherapy, respectively ($P < .01$; Table 3). Of the low-risk cytogenetic changes, ≥ 50 hyperdiploidy occurred similarly (25%) in both groups, and t(12;21) occurred in 11% (five of 46) of the SCT and 28% (23 of 83) of the chemotherapy patients ($P < .05$).

Of the 220 children treated with allo-SCT in 2CR, 110 have died, whereas 110 are alive (Fig 3A). Details on allo-SCT in 2CR have been published.[13,14] In total, 546 children continued receiving chemotherapy (Figs 3A and 4), with a *P* for survival, .39 ± .02, and *P* for EFS in second remission at 10 years (2EFS) of .28 ± .02 at 10 years. In total,

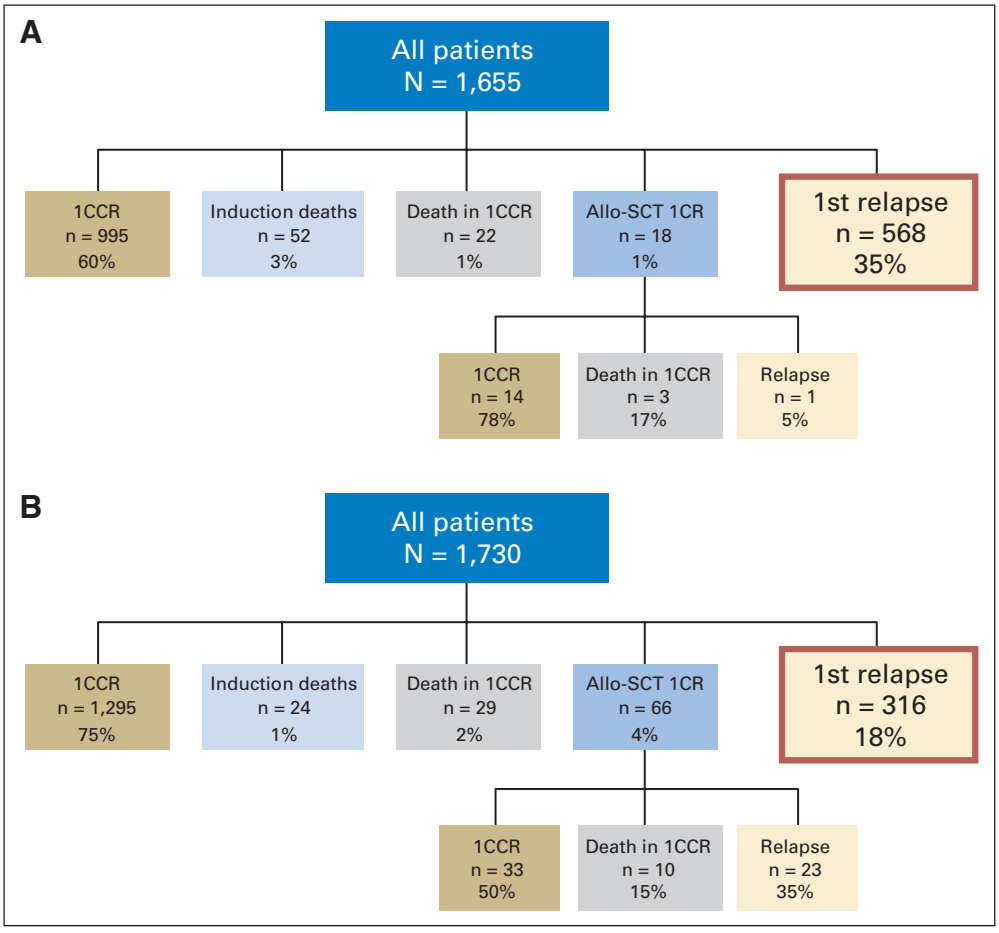

Fig 2. Nordic Society for Pediatric Hematology and Oncology (NOPHO) acute lymphoblastic leukemia (ALL) patients from (A) 1981 to 1991 and (B) 1992 to 2001. The two separate time periods demonstrate the improvements in outcome made. Rough percentages are used due to the long follow-up, (A) 14 to 24 years (minimum 14 years) in and (B) 4 to 14 (minimum) years in, with data frozen for relapses on January 1, 2004. 1CCR, continuous complete first remission; Allo-SCT 1CR, patients who underwent allogeneic stem-cell transplantation in first remission due to very high risk ALL.

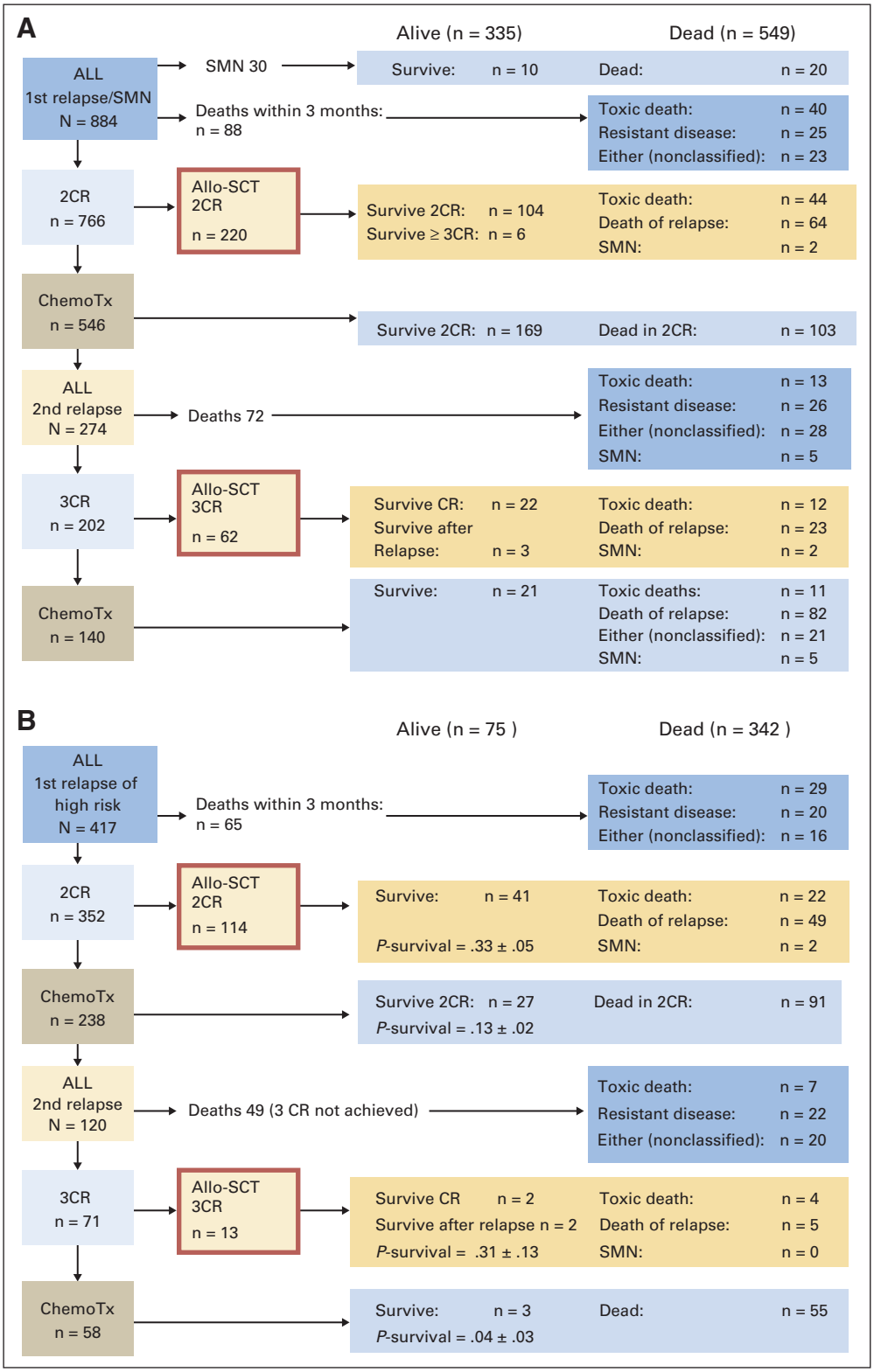

Fig 3. The courses of disease in children with acute lymphoblastic leukemia (ALL) and the first malignant event (n = 884) are shown. Excluded were those younger than 1 or more than 15 years at diagnosis, those with B-ALL, or with allogeneic stem-cell transplantation (Allo-SCT) in first complete remission (1CR). (A) All patients, (B) patients with group 1 relapses only (bone marrow relapses within 36 months of diagnosis). *P* for survival data are estimated at 10 years. SMN, second malignancy; 2CR, second complete remission; chemo TX, chemotherapy; 3CR, third complete remission.

103 patients (19%) have died in 2CR as a result of toxicity, whereas 274 patients (50%) have experienced a second relapse.

Mortality as a result of toxicity was 20% in the transplantation group, and 19% in the chemotherapy group (Fig 4), and the proportion experiencing relapse and death was 30% and 42%, respectively (Fig 4). The 10-year survival in these somewhat dissimilar cohorts was .46 ± .04 in the SCT and .39 ± .02 in the chemotherapy group ($P < .01$).

Table 3. Detailed Characteristics of Patients After First ALL Relapse (n = 854) Divided Into Three Groups: Death Within 3 Months of Relapse (2CR not achieved), Conventional Chemotherapy in 2CR, and Allogeneic SCT in 2CR

Characteristic	Dead < 3 Months (n = 88)		2CR Chemotherapy (n = 546)		2CR SCT (n = 220)		Total (n = 854)		
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	*P**
Age at diagnosis, months									.1
Mean	83		74		79		76		
Median	75		62		66		64		
Sex									.4
Male	62	71	343	63	138	63	543	64	
Female	26		203		82		311		
Initial risk category									< .01
SR	23	26	191	35	62	28	276	32	
IR	15	17	188	34	73	33	276	32	
HR	50	57	167	31	85	39	302	35	
Immunophenotype									< .01
T cell	22	25	49	9	19	9	90	11	
Precursor B	59	67	457	84	192	87	708	83	
ND	7	8	40	7	9	4	56	6	
Time in 1CCR, months									< .01
Mean	17		33		32		31		
Median	12		30		29		28		
1CCR, years									< .01
< 3	79	90	358	66	145	66	582	68	
≥ 3	9		188		75		272		
First relapse category									< .01†
Group 1 (BM relapse and CCR ≤ 36 months)	65	74	238	44	114	52	417	49	
Group 2 (BM negative or CCR > 36 months)	23	26	308	56	106	48	437	51	
Site of BM									
BM	52	59	306	56	137	62	495	58	< .01
BM combined	19	22	76	14	45	21	140	16	
Extramedullary isolated	17	19	164	30	38	17	219	26	
First relapse stratification									< .01†
BM, CCR < 36 months	65	74	238	44	114	52	417	49	
BM, CCR ≥ 36 months	6	7	144	26	68	31	218	26	
Extramedullary, CCR < 36 months	14	16	120	22	31	14	165	19	
Extramedullary, CCR ≥ 36 months	3	3	44	8	7	3	54	6	

NOTE. Percentages are summed vertically within each group of characteristics.
Abbreviations: ALL, acute lymphoblastic leukemia; 2CR, second complete remission; SCT, stem-cell transplantation; SR, standard risk; IR, intermediate risk; HR, high risk; ND, not defined; 1CCR, first continuous complete remission; BM, bone marrow.
*Significance values achieved by comparison among the three groups.
†Significance also valid regarding comparison between 2CR chemotherapy and 2CR SCT only.

Figure 3A and Table 4 illustrate the children who achieved 2CR and received conventional chemotherapy. Age at diagnosis, initial risk category, immunophenotype, time in 1CR, site of first relapse, and first relapse category were all significant prognostic factors in univariate analyses (Table 4). The risk of second relapse or death in 2CR was associated with an early (< 36 months) BM relapse (*P* 2EFS, .11; Fig 5A), initial HR-ALL (*P* 2EFS, .15; Fig 5B), and T-ALL (*P* 2EFS, .10 *v* .30 in precursor B immunophenotype; $P < .01$; Table 4). Combined BM plus extramedullary relapses had an outcome inferior to isolated extramedullary relapses (Fig 5C). Those age ≥ 10 years at diagnosis had a worse prognosis (*P* 2EFS, .15) than those age 3 to 10 years (*P* 2EFS, .27) or 1 to 3 years (*P* 2EFS, .33; $P < .001$). The 103 children who died in 2CR had the worst underlying disease, with 48% of HR-ALL, 21% of T-ALL, and 88% of group 1 category first relapses. In multivariate Cox regression analysis, age at diagnosis, WBC at diagnosis, site of first relapse, and time in 1CR were significant independent factors. In a model using relapse categories combining site and time (BM < 36 months, BM > 36 months, not BM < 36 months, not BM > 36 months, and with four similar categories using 24 months), the combination was the strongest prognostic factor. The initial risk category and immunophenotype did not reach significance as independent factors. Age at relapse, sex, country, or the time period of diagnosis was not significant.

Among late BM relapses and isolated extramedullary relapses, there were subgroups that did not do well. The *P* for 2EFS of those with late (> 36 months) BM relapses but initial HR-ALL (.30 *v* non-HR ALL, .48), *P* for 2EFS of those with on-therapy (< 24 months) extramedullary relapses (.28 *v* > 24 months, .57), and *P* for 2EFS of those with combined BM plus extramedullary relapses (.28; Fig 5C) are suboptimal and inferior to the outcome in more favorable subgroups (Table 4; Fig 5A, 5B, 5C). Outcomes of subgroups, parallel for chemotherapy and allo-SCT, are presented in Table 5.

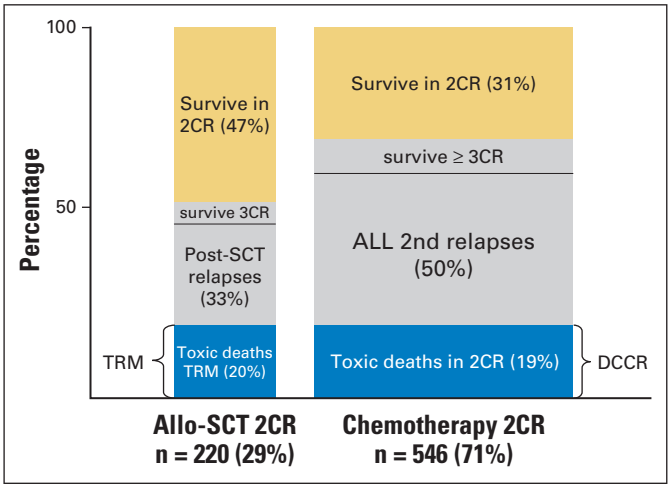

Fig 4. Survivors, relapses, and deaths as a result of toxicity in second complete remission (2CR) of acute lymphoblastic leukemia (ALL; 88 who died < 3 months of first relapse were excluded). The surface areas demonstrate patient groups surviving (light areas), experiencing relapse (shaded areas), or dying as a result of toxicity (dark areas). The small groups of patients experiencing relapse and surviving in ≥ third complete remission (3CR) are indicated. TRM, transplant-related mortality; DCCR, deaths in continuous complete remission; SCT, stem-cell transplantation.

Of the low-risk cytogenetic changes, ≥ 50 hyperdiploidy was seen in 36% *v* 21% ($P < .05$), and t(12;21) was seen in 34% (12 of 35) versus 20% (eight of 39; not significant) of the 2CR survivors versus those with a second relapse, respectively [entire NOPHO data, > 50 hyperdiploidy, 25% to 30%; t(12;21), 22%].

Second Relapse

Of the second relapses (n = 274), 205 (74%) were group 1 (BM) and 69 (36%) were group 2 (BM negative) relapses. Third remission was achieved by 72% (Fig 3A). The remaining 28% died as a result of toxicity (n = 13), resistant leukemia (n = 26), a combination of these (n = 28), or SMN (n = 5; Fig 3A). Those who never achieved 3CR had a shorter first remission, more BM relapses, and shorter time intervals between the relapses, indicating a more aggressive disease (Table 6). Conventional chemotherapy continued in 69% of those who achieved 3CR (Fig 3A). The 20-year survival was 0.12 ± 0.03.

Allo-SCT ≥ 3CR

Allo-SCT was performed in 31% of the 3CR patients (n = 62), constituting 11% of the 546 who continued receiving chemotherapy in 2CR (Fig 3A). This transplantation group (Table 2) had several favorable features, mostly (74%) with SR-ALL or IR-ALL, precursor B immunophenotype (91%), a slow disease with long duration of both 1CR and 2CR, and the first relapse mostly (79%) late or extramedullary (Table 6).

Indications for allo-SCT present already in 2CR were analyzed. Clear SCT indications were recognized in 12 (19%) of 62 patients: BM relapses while receiving therapy (n = 7) or less than 6 months while not receiving therapy (n = 2), extramedullary relapse with T-ALL while receiving therapy (n = 2), and very high risk ALL with WBC more than 400×10^5/L (n = 1). The reasons patients did not receive transplantations were lack of donor (n = 2), lack of time (n = 7; only 2 to 4 months from first to second relapse, all with URDs), and unknown (n = 3). No transplant indication in 2CR was revealed in 16 (26%) of 62 patients with late relapses; nine in BM with SR-ALL, and seven isolated extramedullary. Controversial indications included the 22 patients with late BM relapses (14 IR-ALL, eight HR-ALL), and 12 patients with isolated extramedullary relapses while receiving therapy or less than 6 months while not receiving therapy (not T-ALL or very high risk ALL).

The outcome of this highly selected group was encouraging (Fig 3A), with a 10-year survival *P* of .37 ± .07 ($P < .01$ compared with chemotherapy in 3CR). Twelve patients (19%) died as a result of treatment-related mortality (TRM; GVHD, n = 3; aspergillosis, n = 3; cytomegalovirus pneumonitis, n = 1; sepsis/severe infections, n = 5). Twenty-three patients died as a result of a post-transplantation relapse, and two patients died as a result SMN (brain tumor/primitive neuroectodermal tumor, and Epstein-Barr virus–lymphoma, respectively). Related versus URDs gave similar survival (*P*, .44 *v* .31; $P = .2$).

Summary of Survivors Among Nordic Data

In total, 2,664 of 3,385 patients survive (*P* for survival, .77 ± .01 at 10 years; Table 7). The vast majority (86.0%) continues in 1CR after original chemotherapy, and 190 survive in further remissions. The contribution of allo-SCT recipients (1CR, 2CR, and ≥ 3CR combined) to the bulk of ALL survivors was 184 children (6.9%; Table 7). The outcome after allo-SCT in 1CR, 2CR, and ≥ 3CR is illustrated in Figure 6. The TRM was 15%, 20%, and 19%, and the cumulative post-transplantation relapse rate was 29%, 32%, and 42%, respectively.

Induction Mortality, Remission Mortality, and TRM

Table 8 illustrates all deaths as a result of toxicity among the patients studied. We categorized all induction deaths as deaths as a result of toxicity despite of the possible role of a resistant disease. Mortality on conventional chemotherapy was reduced substantially during the latter time period. Nevertheless, the numbers remained higher (n = 109) than transplantation-related deaths (n = 45). TRM represented only 15% of the deaths as a result of toxicity in total. The TRM for allo-SCT in 1CR, 2CR, and ≥ 3CR combined was 69 (18.9%) of 366.

DISCUSSION

In the population-based Nordic ALL data from 20 years, we analyzed the flow of children through relapses and subsequent remissions before allo-SCT. This analysis illustrates the sites of major patient losses and the points where additional efforts need to be focused.

The pathways leading to allo-SCT in 2CR or ≥ 3CR constitute a remarkable selection process with a progressive loss of patients due to toxicity and an increasingly drug-resistant malignancy (Fig 3A). Understanding this selection process is crucial in evaluating the risks of allo-SCT against those of conventional chemotherapy. We realize that the time period of our material from 1981 through 2001 is not homogeneous with respect to ALL protocols, supportive care, or the SCT indications and donors. However, we considered an extended follow-up essential to allow late and repeat relapses to be included. Patients were lost to induction mortality, which increased from the initial 2% to 10% at the first and 26% at the second ALL relapse (Fig 3A; Table 8). The death rate as a result of toxicity in remission increased from 1% in 1CR to as high as 19% in 2CR.

Table 4. Detailed Characteristics of ALL Patients Who Achieved 2CR and Were Treated With Conventional Chemotherapy

Characteristic	Dead in 2CR (n = 103; 19%)		Second Relapse (n = 274; 50%		Survivors in 2CR (n = 169; 31%)		Total (n = 546; 100%)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Age at diagnosis, months									
Mean	85		76		65				
Median	88		63		55				< .01
Sex									.6
Male	60	58	175	64	108	64	343	63	
Female	43		99		61		203		
Initial risk category									< .01
SR	24	13	89	47	78	41	191	100	
IR	30	16	94	50	64	34	188	100	
HR	49	29	91	54	27	**16**	167	100	
Immunophenotype									< .01
T cell	22	45	22	45	5	**10**	49	100	
Precursor B	76	17	231	51	150	33	457	100	
ND	5	13	21	53	14	35	40	100	
Time in first CCR, months									< .01
Mean	21		31		44				
Median	17		30		40				
1CCR									< .01
< 3 years	96		192		70		358		
≥ 3 years	7	4	82	44	99	**53**	188	100	
First relapse category									< .01
Group 1 (BM relapse and CCR ≤ 36 months)	91	38	120	50	27	**11**	238	100	
Group 2 (BM negative or CCR > 36 months)	12	4	154	50	142	46	308	100	
Site of Relapse									
BM	78	25	160	52	68	**22**	306	100	< .01
BM combined	20	62	32	42	24	32	76	100	
Extramedullary isolated	5	3	82	50	77	47	164	100	
First relapse stratification									< .01
BM, CCR < 36 months	91	38	120	50	27	**11**	238	100	
BM, CCR ≥ 36 months	7	5	72	50	65	45	144	100	
SR	2	3	31	48	31	48	64	100	
IR	4	7	26	46	27	47	57	100	.4
HR	1	4	15	65	7	**30**	23	100	
Extramedullary, CCR < 24 months	4	7	38	64	17	**29**	59	100	
Extramedullary, CCR 24 to < 36 months	1	4	34	56	26	43	61	100	
Extramedullary, CCR ≥ 36 months	0	0	10	23	34	77	44	100	

NOTE. Percentages are summed horizontally within each group of characteristics. Bold font indicates important percentages.
Abbreviations: ALL, acute lymphoblastic leukemia; 2CR, second remission; SR, standard risk; IR, intermediate risk; HR, high risk; ND, not defined; CCR, continuous complete remission; 1CCR, first continuous complete remission; BM, bone marrow.

The use of caution before allogeneic transplants were performed, particularly with URDs, has been based on high TRM rates. For the entire NOPHO-ALL transplant data from 1981 to 2001, including transplants in 1CR, 2CR, and ≥ 3CR, the TRM was 18.9% (Table 8); in the 1990s, for ALL in 2CR only, the TRM was approximately 15%, including URDs.[14] There were fewer transplantation-related deaths (n = 69) than remission deaths of patients receiving conventional chemotherapy (1CR plus 2CR, n = 154). If the mortality as a result of toxicity is to include all induction and remission deaths, TRM only represented 15% of the mortality as a result of toxicity in total (Table 8). Thus, mortality as a result of toxicity cannot be prevented by avoiding allo-SCT.

Transplantations in ALL 3CR have had similar[18] or often poorer[19-21] outcome than those in 2CR. Our data showed a post-transplantation 10-year survival of 46% for 2CR and 37% for ≥ 3CR patients (not significant; Fig 6). The patients who underwent transplantation in 2CR and ≥ 3CR represent groups with very different risk profiles, precluding a meaningful comparison. The patients who underwent transplantation in 2CR mostly had BM relapses, and most relapses occurred early (while receiving therapy or within 36 months of diagnosis), with over-representation of HR ALL (Table 3).[13,14] Those who underwent transplantation in 3CR or beyond were a small, highly selected group. These patients mostly had slow disease with favorable features, with a late first relapse and a long interval between the first and second relapses (Tables 2 and 6). Only 19% would have had clear transplantation indications in 2CR.

Major controversy lies in allo-SCT indications in 2CR of ALL. Time and site of the first relapse are powerful prognostic factors.[22] There is broad consensus that children with early BM relapses or relapses while receiving therapy should undergo transplantation, and those with late extramedullary relapses or extramedullary relapses while not receiving therapy should not undergo transplantation. Between the two extremes, differences in views and recommendations exist. For example, recommendations applied

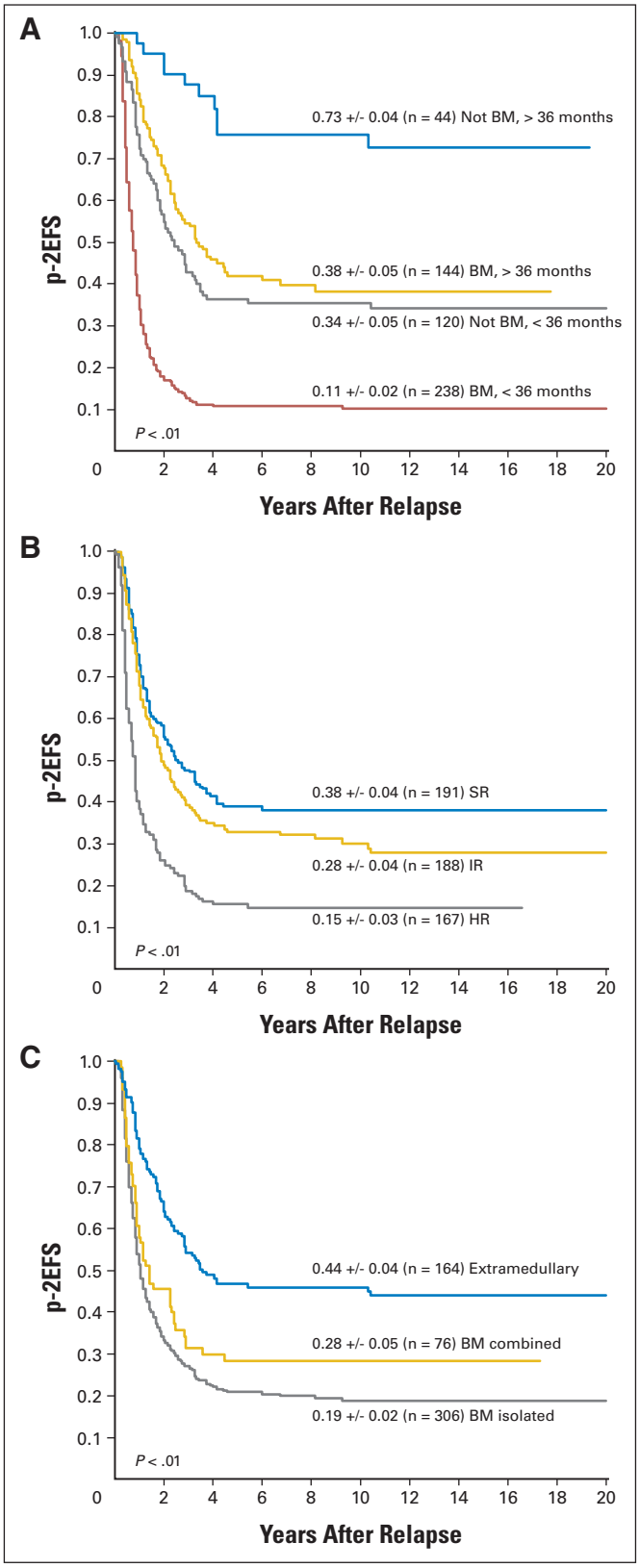

Fig 5. Outcome (*P* for event-free survival [EFS] in second remission at 10 years [2EFS]) of the 546 children who achieved second complete remission (2CR) and continued receiving chemotherapy as a function of (A) time and site combined of the first relapse, (B) the initial risk category, and (C) site of the first relapse. Bone marrow (BM) isolated versus BM combined, $P = .29$; all other comparisons and significance overall, $P < .01$. SR, standard risk; IR, intermediate risk; HR, high risk.

in the United States[6] are not identical to the current German protocol (BFM-Rez 2002, data not published). In the present Nordic data, we especially looked at the 546 children who continued receiving chemotherapy in 2CR (Figs 3A, 3B, 5A, 5B, 5C; Table 4). The patients who experienced relapse or died while receiving chemotherapy were characterized by early (within 36 months) BM relapses, IR or HR ALL, and over-representation of T-ALL. Age older than 10 years at diagnosis was an unfavorable factor. We found subgroups within the favorable relapse categories who did not do well on conventional chemotherapy after achieving a 2CR. These were the patients with late BM relapses but initial HR ALL, extramedullary relapses while receiving therapy, and combined BM plus extramedullary relapses. Although these groups were small with limited statistical power, we believe that allo-SCT should be considered for these patients. Patients with extramedullary relapses during therapy also had poor outcomes in a recent report from the United Kingdom.[23] Our combined BM relapses did not fare significantly better than those with isolated BM relapses (Fig 5C), in contrast to other studies. Response to relapse induction therapy and minimal residual disease at follow-up are important factors in evaluating allo-SCT indications at present. The 2CR patients destined to continue receiving conventional chemotherapy require frequent minimal residual disease monitoring.

Allocation of patients to SCT versus chemotherapy in second remission (Table 3) indicates that many patients with transplantation indications still continued receiving conventional chemotherapy. Our data clearly demonstrate that if patients with HR relapses did not undergo transplantation in 2CR (Fig 3B), they were likely to die in 2CR or have a subsequent relapse with induction failure. Clearly, the children with transplantation indications in 2CR were not the patients who underwent allo-SCT in 3CR; the latter were a different group of patients with favorable features and slow disease who were believed to have a good outcome with conventional chemotherapy in 2CR. The argument that by offering conventional chemotherapy in 2CR, the patient could later be rescued by allo-SCT in the event of an additional relapse[18,23] has no solid background. The chances for rescue later were unexpectedly small. We emphasize that with transplantation indications present in 2CR, allo-SCT should be pursued even with alternative donors. The long-term quality of life has been good post transplantation.[14]

The remission induction rates decreased from the 98% at the primary induction to 90% at the first and 74% at the second ALL relapse (Fig 3). Others have achieved remission induction rates ranging from 65% to 97% at the first ALL relapse,[7,11,24-33] with lower remission rates in early[11,26,27,29,30,33] and higher rates in late relapses.[11,24,25,28,29,33] Our relapse induction mortality represents 5% of the entire NOPHO ALL data: this result need not be inevitable. Better relapse protocols have to be launched. Within NOPHO, the first Nordic ALL relapse protocol is underway with a response-guided design.

In conclusion, major patient losses occurred through mortality as a result of toxicity, and resistant disease during therapy before allo-SCT. After relapse, more patients were lost to mortality as a result of toxicity while receiving conventional chemotherapy than as a result of TRM. After second relapse, the chance for rescue by allo-SCT in 3CR was minimal. These problems need to be addressed by emphasizing and re-evaluating indications for allo-SCT in 2CR and by improving relapse induction therapy.

Table 5. Outcome of Subgroups Defined According to Time and Site of First Relapse, Initial Risk Category, and Site of First Relapse, Treated in Second Remission With Chemotherapy or Allo-SCT

Characteristic	Chemo-2, From Achieved Remission			SCT-2, From Allo-SCT		
	P 2EFS	SD	No. of Patients	*P* 2EFS	SD	No. of Patients
Site and time of first relapse (Fig 5A)						
BM, < 36 months	.11	.02	238	.32	.05	114
BM, ≥ 36 months	.38	.05	144	.53	.08	68
Extramedullary, < 36 months	.34	.05	120	.62	.10	31
Extramedullary, ≥ 36 months	.73	.04	44	.86	.13	7
Initial risk category (Fig 5B)						
SR	.38	.04	191	.46	.07	62
IR	.28	.04	188	.42	.07	73
HR	.15	.03	167	.43	.06	85
Site of first relapse (Fig 5C)						
BM isolated	.19	.02	306	.36	.05	137
BM combined	.28	.05	76	.45	.08	45
Extramedullary	.44	.04	164	.66	.08	38

NOTE. Statistical comparisons between therapy categories are not valid due to selection bias and timing problems.
Abbreviations: allo-SCT, allogeneic stem-cell transplantation; chemo-2, chemotherapy in second remission; SCT-2, allo-SCT in second remission; *P* 2EFS, event-free survival in second remission at 10 years; SD, standard deviation; BM, bone marrow; SR, standard risk; IR, intermediate risk; HR, high risk.

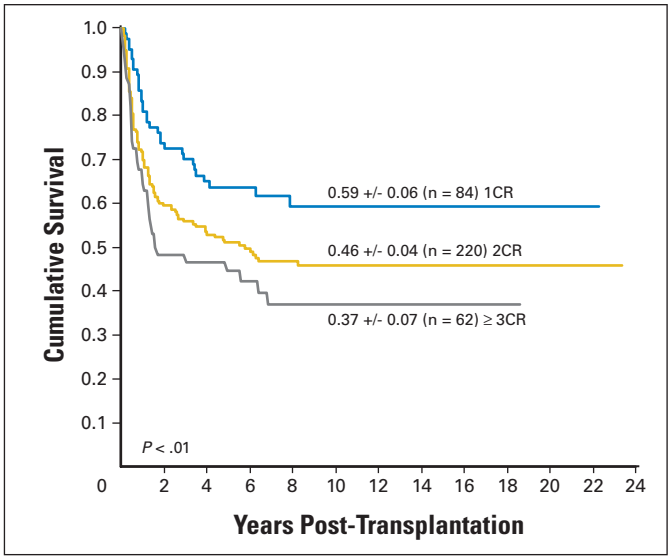

Fig 6. Allogeneic stem-cell transplantation (allo-SCT) of all children in the Nordic Society for Pediatric Hematology and Oncology acute lymphoblastic leukemia (ALL) data (1981 to 2004) who underwent transplantation in first (1CR), second (2CR) or ≥ third complete remission (3CR). Matched sibling/family donors and unrelated donors are pooled together. SCT 2CR *v* 3CR, $P = .23$; SCT 1CR *v* the others, $P < .01$.

Table 6. Detailed Characteristics of Children With Second ALL Relapse (n = 274), Comparing Among Those Who Died and Never Achieved 3CR, Those Treated With Chemotherapy in 3CR, and Those Who Received Allo-SCT in ≥ 3CR

Characteristic	3CR Not Achieved (n = 72)		Chemotherapy in 3CR (n = 140)		Allo-SCT in ≥ 3CR (n = 62)		*P*
	No. of Patients	%	No. of Patients	%	No. of Patients	%	
Status							
Alive	0	0	21	15	25	40	
Dead	72		119		37		
Age at diagnosis, months							.3
Mean	83		71		75		
Median	74		58		66		
Sex							NS
Male	53	74	85	61	37	60	
Female	19		55		25		
Initial risk category							.2
SR	18	25	51	36	20	32	
IR	23	32	45	32	26	42	
HR	31	43	44	31	16	26	
Immunophenotype							.2
T cell	9	13	9	6	4	6	
Precursor B	57	79	117	84	57	91	
ND	6	8	14	10	1	2	
1CCR, years							< .01
< 3	60	83	101	72	31	50	
≥ 3	12		39		31		
First relapse category							< .01
Group 1 (BM relapse and CCR < 36 months)	49	68	58	41	13	21	
Group 2 (BM negative or CCR ≥ 36 months)	23	32	82	59	49	79	
Second relapse category							< .01
Group 1 (BM)	65	90	93	66	46	74	
Group 2 (extramedullary isolated)	7	10	47	34	16	25	
Time from diagnosis to second relapse, months							< .01
Mean	36		50		64		
Median	30		44		59		
Time from first to second relapse, months							< .01
Mean	12		18		26		
Median	9		13		22		
< 6	25	35	29	21	9	15	
≥ 6	47		111		53		< .01
< 24	67	93	100	71	34	55	
≥ 24	5		40		28		< .01

NOTE. Percentages are summed vertically within each group of characteristics.
Abbreviations: ALL, acute lymphoblastic leukemia; 3CR, third complete remission; allo-SCT, allogeneic stem-cell transplantation; NS, not significant; SR, standard risk; IR, intermediate risk; HR, high risk; ND, not defined; 1CCR, first continuous complete remission; BM, bone marrow.

Table 7. Survivors Among 3,385 Nordic Children With ALL Diagnosed During 1981-1991 and 1992-2001

Characteristic	Time Period: 1981-1991 (n = 1,655) No. of Survivors	%	1992-2001 (n = 1,730) No. of Survivors	%	Total (n = 3,385) No. of Survivors	%
1CCR, chemotherapy	995	83.5	1,295	88.0	2,290	86.0
Allo-SCT in 1CR	14	1.2	33	2.2	47	1.8
2CR, chemotherapy	109	9.1	60	4.1	169	6.3
Allo-SCT in 2CR	47	3.9	65	4.4	110	4.2
≥ 3CR, chemotherapy	14	1.2	7	0.5	21	0.8
Allo-SCT in ≥ 3CR	13	1.1	12	0.8	25	0.9
Survivors in total	1,192	72.0*	1,472	85.1*	2,664	78.7*
P for survival	.72		.83		.77	
SD	.01		.01		.01	
Allo-SCT in total	74	6.2	110	7.5	184	6.9
Chemotherapy only	1,118	93.8	1,362	92.2	2,480	93.1

Abbreviations: ALL, acute lymphoblastic leukemia; 1CCR, first continuous complete remission; allo-SCT, allogeneic stem-cell transplantation; 1CR, first complete remission; 2CR, second complete remission; 3CR, third complete remission.
*Percentage of total material; other percentages refer to the percentage of survivors.

Table 8. Induction Mortality, Mortality as a Result of Toxicity in Remission, and TRM Among 3,385 Nordic Children Diagnosed During 1981-1991 and 1992-2001

Characteristic	Time Period: 1981-1991 (n = 1,655) No. of Patients	%	1992-2001 (n = 1,730) No. of Patients	%	Total (n = 3,385) No. of Patients	%
Mortality while receiving conventional chemotherapy						
Primary induction	52 of 1,655	3.1	24 of 1,730	1.4	76 of 3,385	2.2
Deaths in 1CR	22 of 1,603	1.3	29 of 1,706	1.7	51 of 3,309	1.5
Induction of first relapse	68 of 568	12.0	20 of 316	6.3	88 of 884	10.0
Deaths in 2CR	82 of 387	21.2	21 of 159	13.2	103 of 546	18.9
Induction of second relapse	57 of 196	29.1	15 of 78	20.8	72 of 274	26.3
Deaths as a result of toxicity beyond second relapse	ND		ND		ND	
Mortality in total	281 of 1,655	17.0	109 of 1,730	6.3	390 of 3,385	11.5
TRM*						
Allo-SCT 1CR	3 of 18	16.7	10 of 66	15.2	13 of 84	15.5
Allo-SCT 2CR	20 of 101	19.8	24 of 119	20.2	44 of 220	20.0
Allo-SCT ≥ 3CR	1 of 35	2.9	11 of 27	40.7	12 of 62	19.4
TRM in total	24 of 154	15.6	45 of 212	21.2	69 of 366	18.9
Deaths as a result of toxicity in total					459 of 3,385	13.5†
TRM					69 of 459	15.0‡

Abbreviations: TRM, transplantation-related mortality; 1CR, first complete remission; 2CR, second complete remission; ND, not defined; allo-SCT, allogeneic stem-cell transplantation.
*Percentages are of those patients who underwent transplantation.
†Percentage of entire data set.
‡Percentage of deaths as a result of toxicity.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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