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Acute Lymphoblastic Leukemia • Research Paper

Allogeneic stem cell transplantation in acute lymphoblastic leukemia and non-Hodgkin's lymphoma for patients ≤ 50 years old in first complete remission: results of the EORTC ALL-3 trial

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A B S T R A C T

Background and Objectives. In the EORTC ALL-3 trial, the efficacy of allogeneic transplantation was compared with that of autologous marrow transplantation and maintenance chemotherapy in patients ≤ 50 years who reached CR.

Design and Methods. Among 340 patients who entered the study, 279 were ≤ 50 years old. Out of these, 220 reached CR, 184 patients started consolidation and were HLA typed; 68 had a donor and 116 had no sibling donor. The median follow-up was 9.5 years; 93 patients relapsed, 26 died in CR, and overall 116 patients died. Allogeneic transplantation was performed in 47 (68%) patients with a donor while autologous transplantation or maintenance chemotherapy was given to 84 (72%) patients without a sibling donor.

Results. The 6-year disease-free survival rate was similar in the groups with and without donor [38.2% (SE=5.9%) vs. 36.8% (SE=4.6%), hazard ratio 1.01, 95% CI 0.67-1.53]. Comparing the *donor* group with the *no donor* group, the former had a lower relapse incidence (38.2% vs. 56.3%, *p*=0.001), but a higher cumulative incidence of death in CR (23.5% vs. 6.9%, *p*=0.0004). The 6-year survival rates were similar [41.2% (SE=6.0%) vs. 38.8% (SE=4.6%)].

Interpretation and Conclusions. This trial did not show that allogeneic transplantation, when a sibling donor is available, produces a better outcome than the policy of offering autotransplantation or chemotherapy in the absence of a donor.

Key words: allogeneic stem cell transplantation, ALL.

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About 80% of adult patients with acute lymphoblastic leukemia (ALL) can obtain a complete remission (CR),[1-3] but only 30-35% of patients are long-term leukemia-free survivors. In recent years a number of attempts have been made to improve the outcome by using more intensive chemotherapy. Remission-induction therapy (IT) has been intensified by increasing the dose of cyclophosphamide, cytarabine and methotrexate or by adding new drugs.[4-7] The aim of this approach is to destroy leukemia cells before they develop selective drug resistance. More rapid cytoreduction during the induction treatment may not increase the already high CR rate, but may produce longer remissions. Consolidation with high dose Ara-C and/or methotrexate has definitely improved the prognosis of patients with certain subsets of ALL (mature B, T-ALL, pro-B ALL),[8] but it is of unproven or no value in other subsets.[9] Allogeneic stem cell transplantation (allo-SCT) has been shown to be more valuable than autologous stem cell transplantation (auto-SCT) in younger patients with poor prognosis ALL (Ph+ ALL).[10,11] Not giving long-term maintenance treatment is probably detrimental in certain subgroups of ALL (common/pre-B ALL) but randomized trials have never been performed. The degree of intensity of the maintenance regimen has no clear impact on prognosis for the whole group of patients with ALL, but information on its value in subgroups of ALL is not available.[12] The current policy is not to use a single protocol for all adult patients with ALL, but to use different protocols, applied to well defined risk groups, once the patients have achieved complete remission.[13-16] The main goal of the ALL-3[17] study was to determine

Figure 1. EORTC ALL-3 protocol: study design.
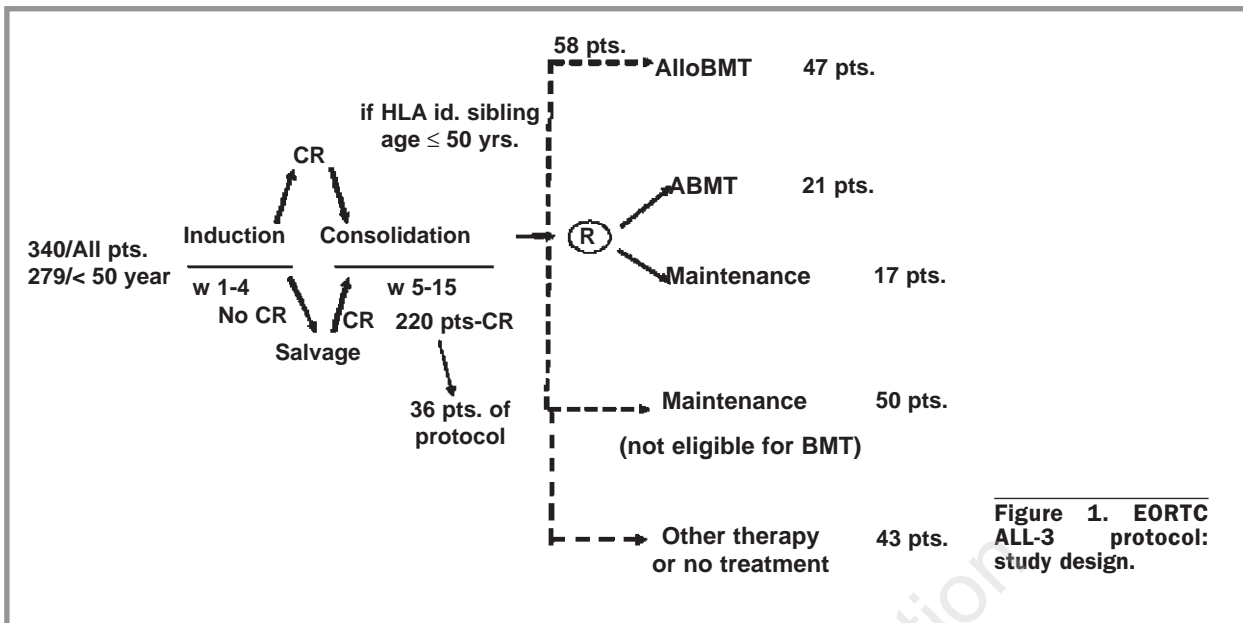
the efficacy of more intensive postremission therapy for adult patients with ALL or non-Hodgkin's lymphoma (NHL). The study protocol included high dose Ara-C consolidation and randomization between an intensive maintenance regimen and autologous bone marrow transplantation. Patients with an HLA-identical family donor were assigned to undergo allogeneic transplantation. In this intention-to-treat analysis the efficacy of allogeneic transplantation was assessed in comparison with that of autologous marrow transplantation or maintenance chemotherapy.

Design and Methods

Study design

The EORTC ALL-3 protocol was approved by the EORTC Protocol Review Committee and by the Ethical Committee of each participating center. This study was conducted from November 1986 to November 1996 in 20 European centers. Patients older than 15 years of age and younger than 60 years of age with *de novo* ALL and lymphoblastic non-Hodgkin's lymphoma (NHL) were included in the study. The randomization was done centrally at the EORTC Data Center, using a minimization technique. The stratification factors were the center and the patient's age. Patients with severe heart, lung, liver, kidney or neurological diseases were ineligible. The study design is presented in Figure 1. All patients received remission induction therapy consisting of daunomycin (45 mg/m^2 on days 1, 2 and 3), cyclophosphamide (600 mg/m^2 on days 1 and 8), vincristine (1.5 mg/m^2 on days 1, 8, 15 and 22), prednisone (60 mg/m^2 orally in three divided doses from day 1 to 22, then tapered over one week), and inthrathecal methotrexate (12 mg on days 1, 8, 15 and

22). If complete remission was not achieved by day +28 salvage therapy was administered. This salvage therapy consisted of cytosine arabinoside (1 g/m^2 given as a 2-hour infusion every 12 hours, 12 times in 6 days) and m-amsacrine (120 mg/m^2 in a one-hour infusion on days 5, 6 and 7 after the beginning of salvage therapy). All patients who achieved CR were given a course of consolidation consisting of L (*E. Coli* 1000 IU/kg, three times a week for two weeks), followed by cyclophosphamide (1 g/m^2 i.v. as a bolus injection), and methotrexate (12 mg intrathecally). Two weeks after administration of cyclophosphamide patients received cytosine arabinoside (1 g/m^2 every 12 hours) for 6 days. Patients with a sibling donor younger than 51 years of age were assigned to undergo allo-SCT. All patients without such a donor, younger than 51 years, were randomized to receive either auto-SCT or maintenance chemotherapy. Patients not eligible for allo-SCT or for randomization received the same maintenance chemotherapy. Maintenance chemotherapy consisted of 2 successive phases: a high dose and a low dose maintenance phase. During the high maintenance phase patients received 6 courses of 10 weeks therapy starting with prednisone (60 mg/m^2/day for 8 days) and vincristine (1.5 mg/m^2/day, days 1 and 8). Doxorubicin (60 mg/m^2 on day 15) was given in courses 1, 3 and 5, while patients received BCNU (80 mg/m^2 day 15) and cyclophosphamide (800 mg/m^2 day 15) in courses 2, 4 and 6. From day 29 until day 58 treatment was 6-mercaptopurine (90 mg/m^2/day), intrathecal methotrexate (day 29) for a total dose of 12 mg and oral methotrexate (20 mg/m^2/weekly). On day 64 actinomycin-D 1 mg/m^2/day was administered. Two weeks after the last course, low maintenance dose was started. This consisted of oral administration of 6-mercaptopurine and

methotrexate as in the high dose maintenance. Every 3 months vincristine (1.5 mg/m^2 on days 1, 8 and 15) and prednisone (40 mg/m^2 orally days 1 to 15) were administered.

The recommended conditioning regimen for allogeneic and autologous transplantation was cyclophosphamide (60 mg/kg on 2 consecutive days) and total body irradiation, fractionated over three days, for a total dose of 1200 cGy. The graft-versus-host disease prophylaxis in most centers was cyclosporine and short course of methotrexate.[18] T-cell depletion of the allogeneic graft was performed in 26 cases by elutriation.[19]

The majority of patients with Ph$^+$ ALL were excluded after achievement of CR and were treated in a separate protocol.

Patients

Between November 1986 and November 1996 340 patients were registered in the ALL-3 study. Of the 279 patients younger than 51 years of age, 220 (79%) achieved CR after induction remission, with or without salvage therapy (Figure 1). Of these patients, 36 were off–protocol treatment due to toxicity or other reasons. Of the remaining 184 patients who started the consolidation, 68 had an HLA-identical sibling donor (*donor* group) and 116 had no family donor (*no donor* group) (Figure 1). In the group without a donor 38 patients were randomized to receive either auto-SCT (n=21) or maintenance chemotherapy (n=17). An additional 50 non-randomized patients, 40 in the *no donor* group and 10 in the *donor* group, started the same maintenance chemotherapy (Figure 1). Other patients (32 in the *no donor* and 11 in the *donor* group) received some other types of chemotherapy or no treatment at all. The median follow-up was 9.5 years with a range from 1 to 15 years.

Evaluation criteria

Complete remission was defined as a morphologically normal marrow with less than 5% blasts, and normal peripheral blood and differential counts. Among patients who reached CR, relapse was defined as > 5% blasts in the bone marrow. A diagnosis of extramedullary relapse was based on tissue diagnosis in case of clinical symptoms or organ or tissue infiltration and cerebrospinal fluid cytology in case of meningeal relapse. Risk factors were defined according to Gökbuget *et al.*[20]

Statistical analysis

The disease-free survival (DFS) was calculated from the date of CR until the date of first relapse or of death in first CR. The time to relapse and time to death in CR were calculated as the DFS; patients who died in CR and those who relapsed were respectively censored at that moment for these 2 analyses. By definition all patients who died in CR were considered as cases of treatment-related mortality (TRM). The duration of survival was calculated from the date of CR until the date of death; patients still alive were censored at their last follow-up. For the comparison of the outcome according to the randomization group (auto-SCT versus maintenance), the starting point was the date of randomization.

Actuarial curves were calculated according to the Kaplan-Meier technique.[21] The standard errors (SE) of the estimates were computed using the Greenwood formula.[21] The estimates of the incidence of relapse and of death in CR, and their corresponding standard errors, were obtained using the cumulative incidence method, in which the risks of death in CR and of relapse were considered as competing risks.[21] The statistical significance of differences between actuarial curves was tested using the two-tailed log-rank test,[21] whereas the Gray test was used for the cumulative incidences.[22] A Cox proportional hazards model was used to obtain the estimate and the 95% confidence interval (CI) of the hazard ratio (HR) of the instantaneous event rate in one group compared with in another group, as specified by a given variable, and the Wald test was used to determine the prognostic significance.[21] This model was also used to determine the relative prognostic importance of several factors. All analyses were based on the intent-to-treat principle.

The database was frozen in August 2002. SAS 8.2 statistical software (SAS Institute Inc, Cary, NC, USA) was used.

Results

Table 1 presents the patients' characteristics according to donor availability. The distributions of the patients' age and sex were similar in both groups. The majority of patients (88%) had ALL, and a mediastinal mass was present in more than 50% of the patients in both groups. Immunophenotyping revealed a trend towards a higher incidence of B-lineage ALL in the *donor* group. About two-thirds of patients in both groups fulfilled criteria for high-risk disease and in about 40% of patients the WBC at diagnosis was high (30×10^9/L). Only 6% of patients with Ph$^+$ -ALL in both groups were treated according to this protocol. No cytogenetic data were available in about 30% of patients.

Relationship between donor availability and stem cell transplantation

In the *donor* group, allogeneic bone marrow transplantation was performed in 47 (69%) patients (Table 2). Ten (15%) patients received maintenance chemo-

Table 1. Patient characteristics for all eligible patients and for patients ≤ 50 yrs, who reached CR, according to donor availability.

	All patients N = 340 (%)	Patients ≤ 50 yrs old, who achieved CR, and started consolidation	
		No donor N = 116 (%)	Donor N = 68 (%)
Age (yrs)			
Median (range)	33 (14 – 79)	26 (14 – 50)	29.5 (14 – 48)
Age < 35	189 (56%)	79 (68%)	48 (71%)
Age 36-50	90 (27%)	37 (32%)	20 (29%)
Age > 50	61 (18%)	0 (0%)	0 (0%)
Sex			
Male	208 (61%)	82 (71%)	41 (60%)
Female	131 (39%)	34 (29%)	27 (40%)
Disease			
ALL	296 (87%)	102 (88%)	60 (88%)
NHL	44 (13%)	14 (12%)	8 (12%)
Stage I/II	21 (6%)	6 (5%)	4 (6%)
Stage III/IV	23 (7%)	8 (7%)	4 (6%)
Mediastinal mass			
Absent	171 (50%)	48 (41%)	29 (43%)
Present	164 (48%)	67 (58%)	39 (57%)
Immunophenotype			
AUL	3 (1%)	0 (0%)	0 (0%)
B-lineage ALL	141 (41%)	45 (39%)	33 (50%)
Pro-B	20	7	4
Common ALL	49	11	16
Pre-B	14	3	6
cALL or pre-B	42	19	7
Mature-B	16	5	0
T-lineage ALL	45 (13%)	19 (16%)	13 (19%)
Pro-T	18	11	2
Pre-T	23	7	11
Mature-T	4	1	0
Bi-pheno./AML	4 (1%)	1 (1%)	0 (0%)
NHL	23 (7%)	8 (7%)	5 (7%)
N. eval./Unknown	124 (36%)	43 (37%)	17 (25%)
Risk group			
Standard	58 (17%)	28 (24%)	19 (28%)
High*	271 (80%)	88 (76%)	49 (72%)
WBC (×10⁹/L)			
< 30	224 (66%)	73 (63%)	38 (56%)
≥ 30	111 (33%)	43 (37%)	29 (43%)
Cytogenetics			
Ph positive	30 (9%)	7 (6%)	4 (6%)
Others/Normal	195 (57%)	69 (60%)	43 (63%)
Unknown	115 (34%)	40 (34%)	21 (31%)

*: WBC 30¥109/L, age > 35 years, immunophenotyping AUL, CR reached > 4 weeks, or other criteria according to the local centers.N. eval.: not evaluated.

Table 2. Treatment applicability after consolidation for all patients who reached CR and for patients ≤ 50 yrs according to donor availability.

	All CRs N= 253* (%)	Patients ≤ 50 yrs old, who achieved CR, and started consolidation	
		No donor N= 116 (%)	Donor N= 68 (%)
Treatment in CR1			
AutoBMT	30 (12%)	27 (23%)	0 (0%)
AlloBMT	49 (19%)	0 (0%)	47 (69%)
Maintenance	79 (31%)	57 (49%)	10 (15%)
Other treatment	31 (12%)	16 (14%)	4 (6%)
No other treatment	64 (25%)	16 (14%)	7 (10%)

*:223 patients received consolidation; 2 patients have been allografted just after induction.

Table 3. Treatment outcome for all patients and for patients ≤ 50 yrs who reached CR, and started the consolidation, according to donor availability.
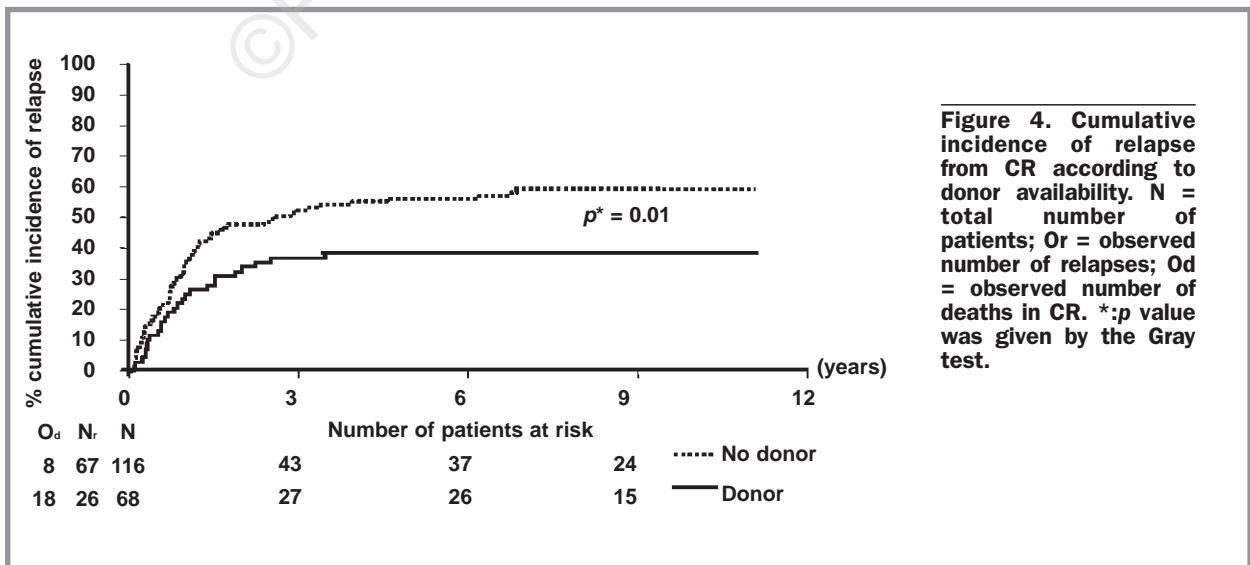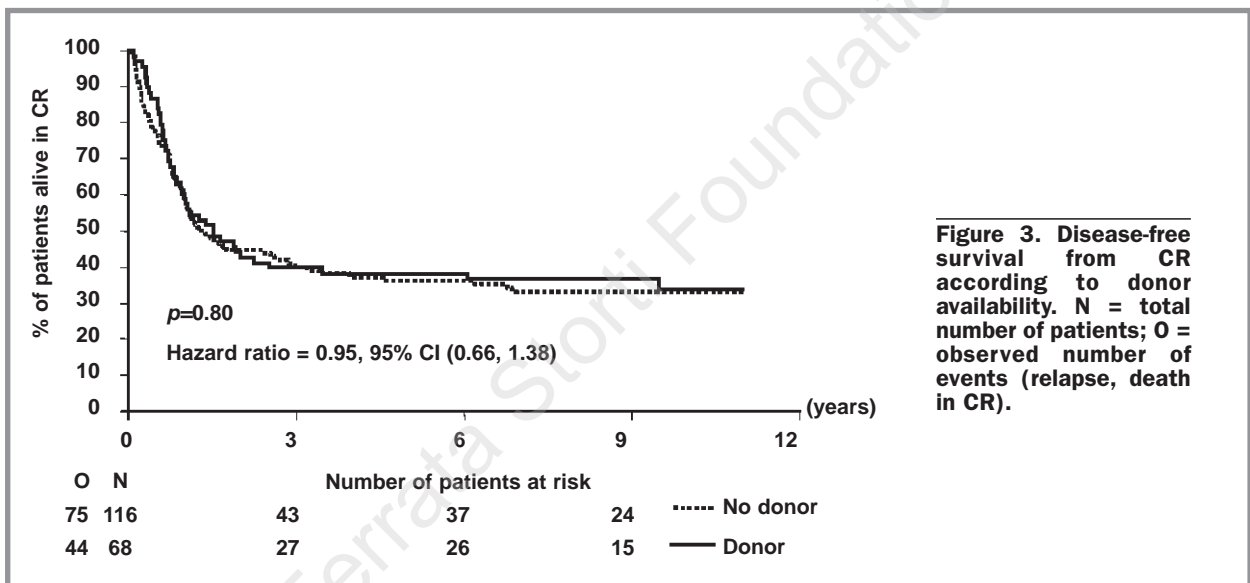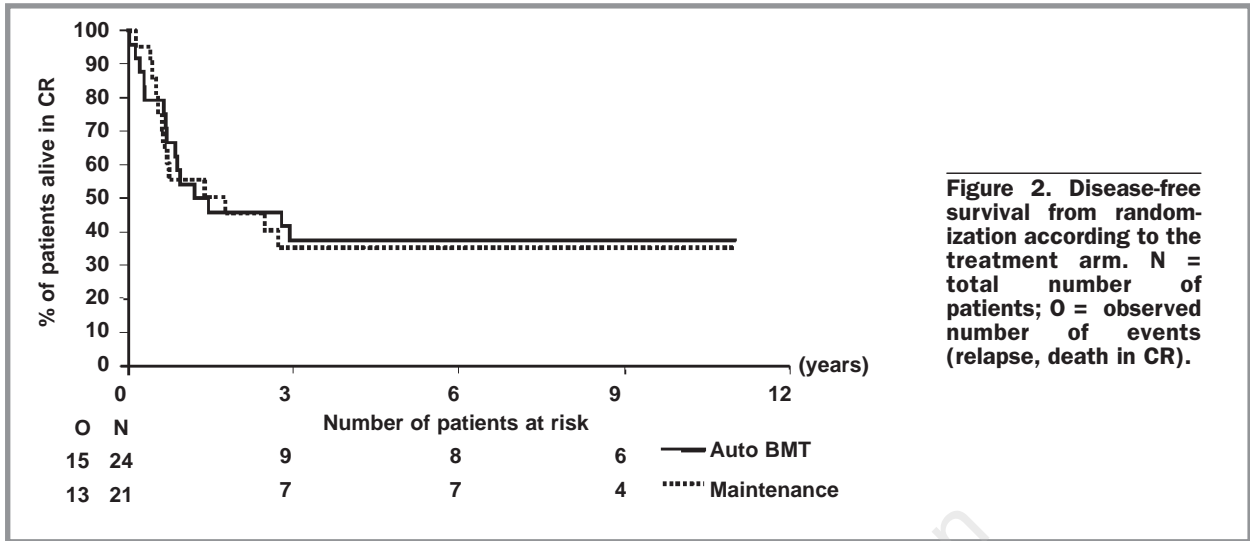
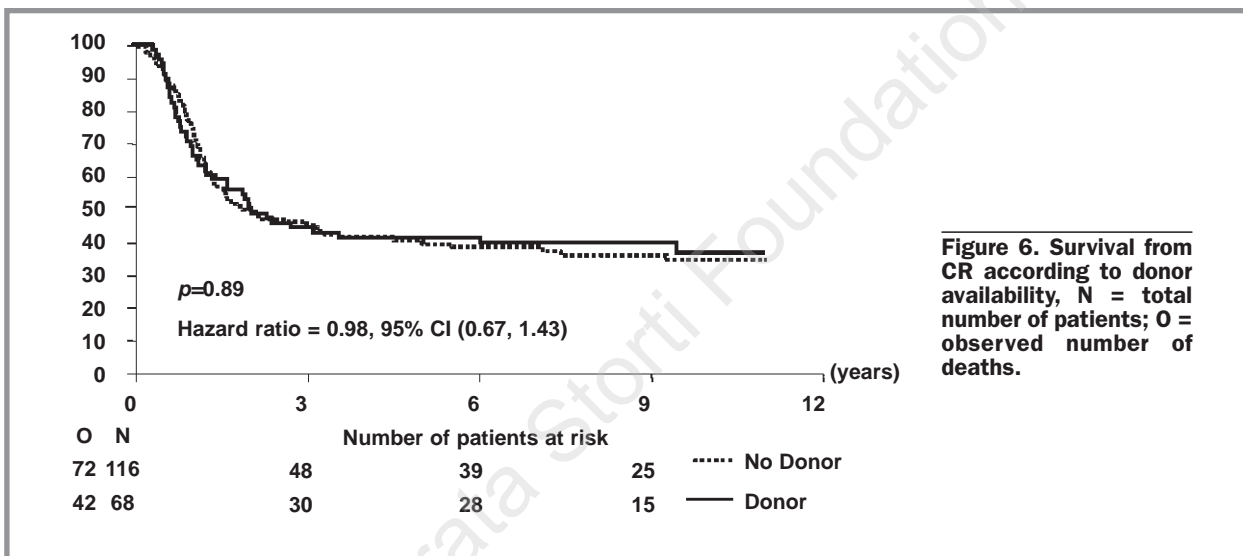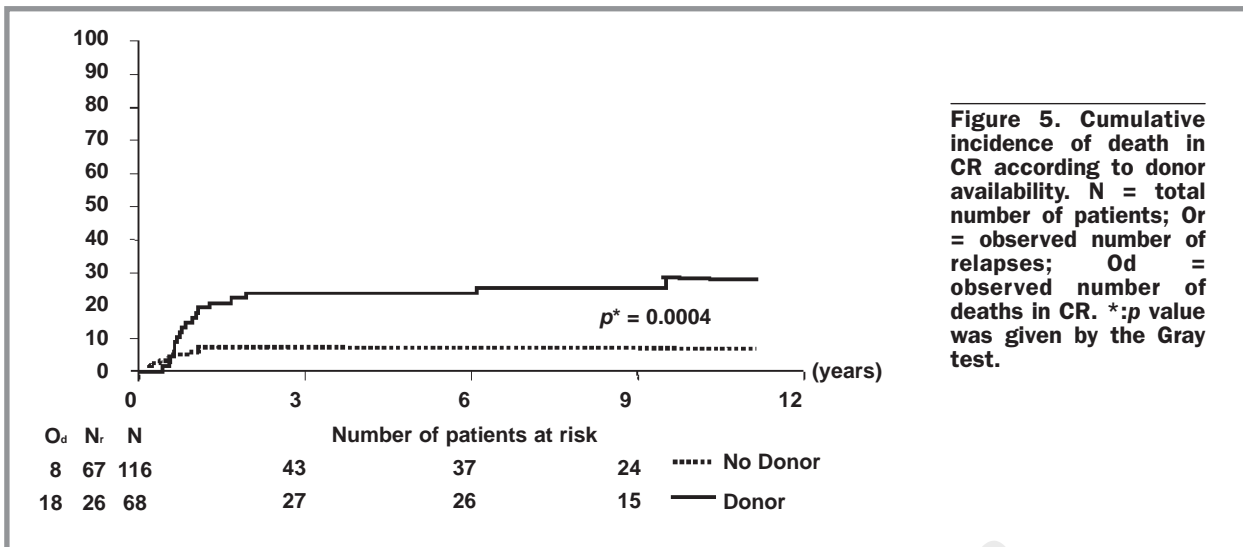|	All patients N = 340 (%)	Patients ≤ 50 yrs old, who achieved CR, and started consolidation	
		No donor N = 116 (%)	Donor N = 68 (%)
CR after induction	228 (67%)	105 (91%)	64 (94%)
CR after induction/ salvage	253 (74%)	116 (100%)	68 (100%)
CR after consolidation	191 (56%)	98 (85%)	60 (88%)
DFS status*			
CCR	80 (24%)	41 (36%)	24 (36%)
Relapse	131 (39%)	67 (58%)	26 (38%)
Death in CR	42 (12%)	8 (6%)	18 (26%)
Survival status			
Alive	95 (28%)	44 (38%)	26 (38%)
Dead	245 (72%)	72 (62%)	42 (62%)

*: in patients who reached CR.

therapy, 4 (6%) received other treatment and 7 (10%) had no further therapy. In the *no donor* group, 27 (23%) patients underwent autologous bone marrow transplantation, 57 (49%) received maintenance chemotherapy, 16 (14%) received other maintenance and 16 (28%) had no further therapy.

Treatment outcome for all patients

Treatment outcome for all patients is given in Table 3. In 253 (74%) out of 340 patients complete remission was achieved after remission induction and/or salvage chemotherapy. CR after consolidation was documented in 191 (56%), and 80 are still in continu–

Figure 2. Disease-free survival from randomization according to the treatment arm. N = total number of patients; O = observed number of events (relapse, death in CR).

O	N				
15	24	9	8	6	Auto BMT
13	21	7	7	4	Maintenance

$p=0.80$

Hazard ratio = 0.95, 95% CI (0.66, 1.38)

Figure 3. Disease-free survival from CR according to donor availability. N = total number of patients; O = observed number of events (relapse, death in CR).

O	N				
75	116	43	37	24	No donor
44	68	27	26	15	Donor

$p* = 0.01$

Figure 4. Cumulative incidence of relapse from CR according to donor availability. N = total number of patients; Or = observed number of relapses; Od = observed number of deaths in CR. *:p value was given by the Gray test.

Od	Nr	N				
8	67	116	43	37	24	No donor
18	26	68	27	26	15	Donor

Figure 5. Cumulative incidence of death in CR according to donor availability. N = total number of patients; Or = observed number of relapses; Od = observed number of deaths in CR. *:p value was given by the Gray test.

Figure 6. Survival from CR according to donor availability, N = total number of patients; O = observed number of deaths.

ous first complete remission; 131 patients relapsed and 42 died in complete remission. The disease-free survival and overall survival rates ($\pm$ SE%) at 6 years for patients who reached 1st CR were 33.5% ($\pm$ 5.9%) and 36.0% ($\pm$ 5.9%), respectively. The corresponding estimated hazard ratios with 95% confidence intervals were 1.11 (95% CI 0-95-1.72) and 1.63 (95% CI 1.29--2.55), respectively. Concerning survival status, 95 (28%) patients are alive, while 245 (72%) patients have died. A total of 45 patients were randomized to receive either autologous bone marrow transplantation (n = 24) or maintenance chemotherapy (n = 21). The disease-free survival was very similar for both groups (Figure 2). The estimated hazard ratio was 1.06 (95% CI 0.50-2.23).

Effect of donor availability on outcome

The DFS was not statistically different (*p*=0.69) between the d*onor* group and the *no donor* group. The 6-year DFS rate for the *donor* group was 38.2 ($\pm$ 5.9%)

versus 36.8% ($\pm$ 4.6%) for the *no donor* group; the estimated hazard ratio was 1.01 (95% CI 0.67-1.53) (Figure 3).

The 6-year cumulative incidence of relapse for the *donor* and *no donor* groups was 38.2% ($\pm$ 6.0%) and 56.3% ($\pm$ 4.7%), respectively (Figure 4), and the 6-year cumulative incidence of death in CR was 23.5% ($\pm$ 5.2%) and 6.9% ($\pm$ 2.4%), respectively (Figure 5).

The duration of survival after CR was not significantly different (*p*=0.80) between the two groups: the estimated hazard ratio was 0.95 (95% CI 0.66-1.38) (Figure 6). The 6-year estimate rate was 41.2% ($\pm$ 6.0%) for the *donor* group and 38.8% ($\pm$ 4.6%) for the *no donor* group. Of the 47 patients in the *donor* group who had an allograft, 12 died early after the transplant and so there are no data on chronic GVHD from these patients; among the remaining 35 patients, chronic GvHD was reported in 12 (34%) patients: the degree of severity was mild (n=8), moderate (n=1) or severe (n=8).

Effect of age and WBC and donor availability on outcome

In this population of patients, all under 51 years old, age was not of prognostic importance (p=0.34), and did not influence the difference between the outcome of the *donor* and *no donor* groups. The comparison of DFS in the *donor* and *no donor* groups, adjusted for age, remained practically unchanged: the estimated hazard ratio was 0.96. For the risk of death in CR, the Cox model showed that age group (HR=2.91, p=0.007) and *donor* availability (HR=3.84, 95% CI 1.67-8.83, p=0.002) were two independent prognostic factors.

Patients with initial low WBC ($< 30\times10^9$/L) had a significantly (p=0.0025) longer DFS than those with a WBC $\geq 30\times10^9$/L: the hazard ratio was 0.59 (95% CI 0.4-0.83), and the 6-year DFS rate was 45.3% ($\pm$ 4.8%) and 25.6% ($\pm$ 5.2%) in the low WBC and high WBC groups, respectively. The difference in outcome between patients with and without a donor remained small in each group; the estimated hazard ratio, adjusted for WBC, remained almost unchanged (0.90), and the 95% confidence interval was 0.62-1.31. For the risk of relapse, the Cox model indicated that WBC group (HR=1.95, p=0.002) and donor availability (HR=0.58, 95% CI 0.37-0.92, p=0.02) were two independent prognostic factors.

Risk group (high versus standard) was not of prognostic importance for DFS. Differences were not detected between the *donor* and *no donor* groups in standard risk patients (HR=0.82, 95% CI 0.37-1.83) or in high risk patients (HR=1.04, 95% CI 0.68-1.59).

Discussion

This intention-to-treat analysis concerning the whole group of ALL patients under the age of 51 years did not prove any advantage for allogeneic transplantation compared with autologous transplantation or chemotherapy for patients treated according to EORTC ALL-3 protocol. These results are in line with the retrospective analysis of IBMTR which also showed no difference in outcome between allografting and chemotherapy,[23,24] although some recent data from this Registry did reveal a significantly better DFS for allografted patients younger than 30 years of age compared to those receiving chemotherapy.[25] The French LALA group performed a prospective trial, similar to ours, but in a larger cohort.[26] Patients aged 15 to 40 years, in CR and with an HLA-identical sibling donor, were assigned to be allografted. Those without a donor were randomized to receive either autotransplantation or maintenance therapy. According to intention-to-treat analysis this study showed a better DFS for allografted patients compared to those treated with chemotherapy especially in high risk patients (10-year

survival rate: 44% vs 11%). Some recent reports did not show a better outcome for adult ALL patients with a donor compared to those without a donor.[27]

Our trial confirmed[28,29] that allografting is a more at eradicating leukemia and/or lymphoblastic lymphoma than is autografting and chemotherapy. The relapse rate was significantly lower for the *donor* group than for the *no donor* group (31.7% versus 50.3%). However, the toxicity of allografting was higher than that of other post-remission treatment options. About 30% of patients died in CR because of complications related to allogeneic transplantation such as graft-versus-host disease and serious infections.[30,31]

The known risk factors for treatment outcome, such as tumor mass (WBC more than 30×10^9/L) and the patient's age (> 35 years of age), had no impact on the difference in outcome according to donor availability. Conversely, younger patients with less leukemic mass had a better outcome than the others, and this was independent of the availability or not of a donor. The prognostic importance of other risk factors could not be evaluated properly (e.g. cytogenetics, immunophenotyping) and there were only a very limited number of patients in some categories (e.g.: CR reached only after salvage [n=15]). The majority of patients with Ph-positive ALL had been excluded after achievement of CR and treated in another protocol. Therefore, only 11 Ph-positive ALL patients were included in the *donor* vs. *no donor* comparison.

About 70% of patients with a donor in this trial received an allogeneic transplant, while 30% did not reach this part of the treatment. Most of these patients died before transplantation because of relapse and severe toxicity related to therapy or had become ineligible for the further very intensive treatment at the time of allotransplantation. This trial, as many others,[26,28] proved that allotransplantation is the most efficient therapy in eradicating and controlling leukemia. It might, therefore, be appropriate to perform allotransplantation upfront in the post-remission period, immediately after CR has been achieved. This might decrease treatment-related toxicity, and the drop out of patients because of relapse. More patients with a donor would undergo allografting in a better general condition and in an early phase of disease. This treatment strategy should be applied in high risk group of patients and studied in a randomized prospective trial.

The graft-versus leukemia (GvL) effect has recently been proven to occur in both T- and B-lineage ALL in patients with acute and chronic graft-versus-host disease (GvHD).[32] However, there is no evidence of a GvL effect in ALL patients without GvHD, and this might, in part, explain our results. It is important to stress that the results in this study were obtained in the years 1986 to 1996. Over this long period our knowledge and available treatments have improved substantially,

especially concerning complications and supportive care in allografted patients. Several studies have demonstrated this, showing that transplant results have improved recently mainly due to a decrease in transplant-related mortality. The EBMTG clearly showed significantly better results for patients allografted after 1991 than for those treated before.[33]

In conclusion, this intention-to-treat analysis did not prove that the outcome of patients with ALL and an HLA-identical sibling donor treated according to EORTC ALL-3 protocol was better than that of patients without a sibling donor. The relapse rate in patients with a donor was significantly lower but death in remission was significantly higher for this group of patients. Younger patients with less leukemic mass had the best prognosis independently of donor availability. Improved results of allogeneic transplan-

tation are expected to reduce the treatment-related mortality of this therapeutic approach. This effect may alter the outcome of various treatment approaches assessed in this study.

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