Long-Term Follow-up of Adults with Acute Lymphoblastic Leukemia in First Remission Treated with Chemotherapy or Bone Marrow Transplantation

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■ *Objective:* To determine whether the conclusions of a 1991 study, which showed that adults with acute lymphoblastic leukemia in first remission had similar leukemia-free survival rates when treated with chemotherapy or HLA-identical sibling bone marrow transplantation, remain valid after more than 4 years of additional follow-up.

■ *Design:* Retrospective comparison of two cohorts of patients using left-truncated Cox regression to adjust for differences in baseline characteristics and time to treatment.

■ *Setting and Patients:* Chemotherapy recipients were 484 consecutive patients with acute lymphoblastic leukemia in first remission treated in 44 hospitals in Germany that were participating in two consecutive trials of the German Acute Lymphoblastic Leukemia Therapy Trials Group. Transplant recipients were 234 consecutive recipients of HLA-identical sibling bone marrow transplants for acute lymphoblastic leukemia in first remission in 98 centers, worldwide, reporting data to the International Bone Marrow Transplant Registry.

■ *Interventions:* Intensive combination chemotherapy or HLA-identical sibling bone marrow transplantation preceded by high-dose chemotherapy with or without total body irradiation.

■ *Measurements:* Relapse, treatment-related mortality, and leukemia-free survival rate 9 years after first complete remission.

■ *Results:* The conclusions of our previous analyses were confirmed. Actuarial relapse probabilities at 9 years were 66% (95% CI, 61% to 70%) for chemotherapy and 30% (CI, 22% to 37%) for transplantation ($P < 0.0001$). The leukemia-free survival rates at 9 years were 32% (CI, 27% to 37%) for chemotherapy and 34% (CI, 28% to 40%) for transplantation ($P > 0.02$).

■ *Conclusions:* Fewer relapses but more treatment-related deaths were seen with transplantation than with chemotherapy. Thus, leukemia-free survival rates were similar in adults receiving transplantation and adults receiving chemotherapy for acute lymphoblastic leukemia in first remission.

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Considerable controversy exists about whether chemotherapy or HLA-identical sibling bone marrow transplantation is the best therapy for adults with acute lymphoblastic leukemia in first remission (1–3). Our 1991 study (1) compared 454 adults receiving chemotherapy with 234 adults receiving transplants. Chemotherapy recipients were treated in 44 hospitals in Germany in two consecutive trials of the German Acute Lymphoblastic Leukemia Therapy Trials Group. Transplantations were done in 98 centers, worldwide, that reported data to the International Bone Marrow Transplant Registry. Using statistical methods to adjust for leukocyte count at diagnosis, immune phenotype, time to first complete remission, and time to treatment, we found fewer relapses but higher treatment-related mortality with transplantation. Leukemia-free survival rates at 5 years were similar (about 40%) with the two treatments; this was true for both patients with favorable and patients with unfavorable risk factors. The median follow-up when the study was published was 3 years.

Although the conclusions of that study were clear, there was speculation that a difference favoring transplantation might emerge with additional follow-up. This hypothesis was based on the prediction that persons receiving chemotherapy would continue to have relapses, whereas relapse would not occur or would occur less frequently in the transplantation cohort.

This current study, which has a median follow-up of 7.5 years, updates our previous report and shows that 9-year leukemia-free survival rates were similar in patients treated with these two therapies.

Methods

Details of our previous analysis have been published (1). The previous study included two series of consecutively treated patients. The chemotherapy cohort comprised 484 patients treated in two multicenter trials in Germany (January 1981 and February 1984) who achieved complete remission of acute lymphoblastic leukemia between 1 January 1980 and 30 June 1987 (4, 5). The transplantation cohort comprised 234 patients with acute lymphoblastic leukemia in first remission who received bone marrow

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transplants from HLA-identical siblings between 1 January 1980 and 30 June 1987 and for whom complete information about prognostic factors was available. These patients had had no bone marrow or extramedullary relapse before transplantation. Data were reported to the International Bone Marrow Transplant Registry by 98 teams (6). Analysis was restricted to patients between 15 years of age (the lower age limit for the chemotherapy trials) and 45 years of age (the age of the oldest person in the transplantation cohort) at the time of treatment. Patients with B-cell acute lymphoblastic leukemia and hybrid leukemia (7) were excluded because there were so few of them. Details of the two cohorts and their treatments have been previously described (1).

Median follow-up at the time of this study was 7.5 years (range, 0.1 to 13.5 years); it was 7.0 years (range, 0.1 to 13 years) in the chemotherapy cohort and 8.3 years (range, 2.3 to 13.5 years) in the transplantation cohort.

Outcome

The primary end point was duration of leukemia-free survival (survival without recurrent leukemia) after first remission. Patients were considered treatment failures at time of relapse or at time of death from any cause and were censored only at time of last follow-up. Probabilities of relapse and treatment-related deaths were also determined. Recurrence of leukemia was defined in both cohorts as recurrence of more than 5% lymphoblasts in the bone marrow or detection of leukemia cells in the blood or extramedullary sites. In estimations of probabilities of relapse, patients in continuous complete remission were censored at time of death from nonleukemic causes or at time of last follow-up. Treatment-related deaths were defined as deaths occurring in patients in continuous complete remission after treatment; these patients were censored at time of relapse or at time of last follow-up.

Statistical Analysis

Comparison of transplantation and chemotherapy requires adjustment for two sources of bias: 1) differences in the baseline characteristics of patients chosen for each treatment and 2) a difference in time to treatment in the two cohorts. To address the second source of bias, which arises because patients in the transplantation cohort must survive in remission long enough for transplantation to be done, we used a left-truncated Cox regression model to estimate the effects of covariates on treatment-related mortality, relapse, and leukemia-free survival (8, 9). Using this method, the risk set at each time point in the chemotherapy cohort consists of all patients in the initial cohort still being studied. In the transplantation cohort, the risk set at each time point includes only those who had a waiting time to transplantation of less than the current time point and who are still being studied. We adjusted for differences in baseline characteristics by including as fixed covariates factors predictive of leukemia-free survival in stepwise regression analysis of all patients using the left-truncated Cox model. The following factors were correlated with outcome: age, immune phenotype (T-cell or others), leukocyte count at diagnosis ($\log_e$), and time to first remission. Other potential prognostic factors considered but not significant in the stepwise analyses were the presence of a mediastinal mass at diagnosis ($P = 0.22$) and year of diagnosis ($P = 0.32$). We tested for interaction between significant covariates and type of treatment and found that the effect of leukocyte count at diagnosis differed in the two cohorts. A high leukocyte count at diagnosis had a greater negative effect on leukemia-free survival in the chemotherapy than in the transplantation cohort. Hence, in the final models, single covariates were used for age, immune phenotype, and time to remission, whereas separate covariates by treatment type were used for leukocyte count at diagnosis. Transplantation was considered to be a time-dependent covariate: Treatment effect differed for 12 or fewer months after first remission compared with more than 12 months after first remission.

Adjusted probabilities of treatment-related mortality, relapse, and leukemia-free survival were generated from the above Cox models using the mean covariate value for each prognostic factor from the pooled sample (10). Odds ratios are based on these estimated probabilities. For subgroup analysis, the basic Cox model was refit to the data in specified groups. In all cases, reported probabilities represent predicted outcomes for similar groups of patients receiving each treatment. *P* values for comparison of survival probabilities at fixed points in time are based on the standardized difference in estimated survival obtained from fitted Cox models in the two groups.

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Results

Adjusted probabilities of treatment-related mortality at 9 years were 5% (95% CI, 3% to 7%) for persons receiving chemotherapy and 53% (CI, 45% to 61%) for persons receiving transplants ($P < 0.0001$). Most treatment-related deaths occurred within 1 year of treatment. Among patients surviving in remission for 3 years, the probability of treatment-related death in the subsequent 6 years was 1% (CI, 0% to 2%) with chemotherapy and 9% (CI, 3% to 15%) with transplantation ($P = 0.01$).

Adjusted probabilities of relapse at 9 years were 66% (CI, 61% to 70%) for persons receiving chemotherapy and 30% (CI, 22% to 37%) for persons receiving transplants ($P < 0.0001$). Late relapses occurred in both groups. Among patients surviving in remission for 3 years, the actuarial probabilities of having relapse in the subsequent 6 years were 18% (CI, 12% to 24%) with chemotherapy and 5% (CI, 1% to 9%) with transplantation ($P = 0.0004$). The latest relapses seen occurred at 6.6 years in the chemotherapy cohort and at 4.2 years in the transplantation cohort.

Adjusted probabilities of leukemia-free survival at 9 years for persons receiving chemotherapy or transplants are shown in Table 1. At 9 years, chemotherapy and transplantation did not differ significantly ($P > 0.2$) either in the entire cohort or in groups defined by high- and low-risk prognostic factors. Among patients surviving in remission for 3 years, the probabilities of leukemia-free survival for the subsequent 6 years were 82% (CI, 76% to 88%) for chemotherapy and 87% (CI, 80% to 94%) for transplantation ($P > 0.2$).

Discussion

Our data indicate that HLA-identical sibling transplantation is associated with fewer relapses than chemotherapy in adults with acute lymphoblastic leukemia in first remission. However, 9-year leukemia-free survival rates were similar for the two therapies. This conclusion applies to low- and high-risk groups as defined by leukocyte count at diagnosis, immune phenotype, and time to first remission. The prediction that a difference between chemotherapy and transplantation might emerge with additional follow-up after our 1991 report was not confirmed. Although late relapses were less common in the transplantation cohort, this benefit was insufficient to overcome the increased treatment-related mortality seen with transplantation.

Our conclusions apply to these treatments as given between 1980 and 1987. Little indication of improvement in chemotherapy results has been seen since then. Although some studies suggest modest improvement in transplantation outcome since 1987, it is uncertain

Table 1. Adjusted Probabilities of Leukemia-Free Survival 9 Years after First Remission according to Type of Therapy Received after Remission and Prognostic Factors

Variable	Chemotherapy Group		Transplantation Group		RR (95% CI)*
	Patients	Probability of Leukemia-Free Survival (95% CI)	Patients	Probability of Leukemia-Free Survival (95% CI)	
	n	%	*n*	%	
All patients	484	32 (27 to 37)	234	34 (28 to 40)	0.93 (0.60 to 1.26)
Leukocyte count $\leq 30 \times 10^9$/L†	328	38 (32 to 44)	132	37 (28 to 46)	1.02 (0.57 to 1.47)
Leukocyte count $> 30 \times 10^9$/L	156	23 (16 to 30)	102	30 (20 to 40)	0.68 (0.26 to 1.11)
Time to remission ≤8 wks	395	36 (31 to 41)	156	40 (32 to 48)	0.86 (0.51 to 1.21)
Time to remission >8 wks	89	19 (10 to 28)	78	20 (11 to 29)	0.96 (0.20 to 1.72)
T-cell phenotype	107	39 (29 to 49)	66	46 (33 to 59)	0.74 (0.23 to 1.24)
Non–T-cell phenotype	247	25 (19 to 31)	133	28 (20 to 36)	0.86 (0.44 to 1.29)

* RR = relative risk of treatment failure for patients receiving transplantation compared with chemotherapy.
† At diagnosis.

whether this reflects increased efficacy or patient selection (11). The results of our study are similar in some respects to those recently reported by the French Group for Therapy of Adult Acute Lymphoblastic Leukemia (12). They found similar disease-free and overall survival with transplantation and chemotherapy in a prospective trial, in which patients with an HLA-identical sibling were assigned to receive a transplant. In contrast to our study, this study showed an advantage for transplantation in high-risk patients (5-year leukemia-free survival rate, 39% [CI, 23% to 55%] compared with 14% for chemotherapy [CI, 4% to 24%]; $P = 0.01$). Five-year leukemia-free survival rates in our study were 33% (CI, 26% to 40%) with transplantation and 31% (CI, 26% to 36%) with chemotherapy. The reasons for the difference in chemotherapy outcome in the two studies are not clear. The French Group study was more recent (it began in 1986), used different chemotherapy, and used slightly different high-risk criteria, including cytogenetics. Cytogenetic data were available for few patients in our study. Data from both studies support reserving transplantation for treatment of relapse in adults with standard-risk acute lymphoblastic leukemia who have relapse.

In conclusion, we found fewer relapses but more treatment-related mortality with HLA-identical sibling transplantation than with chemotherapy. Thus, leukemia-free survival rates were similar in adults receiving transplantation and adults receiving chemotherapy for acute lymphoblastic leukemia in first remission.

Appendix

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