Allogeneic Hematopoietic Stem Cell Transplantation as Part of Postremission Therapy Improves Survival for Adult Patients with High-Risk Acute Lymphoblastic Leukemia

A Metaanalysis

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BACKGROUND. The prognosis for adult patients with acute lymphoblastic leukemia (ALL) remains unsatisfactory primarily because of the high incidence of recurrence. Therefore, optimal postremission therapy is a matter of vital concern. In particular, the clinical efficacy of allogeneic hematopoietic stem cell transplantation (HSCT) should be clarified.

METHODS. Rigorous criteria were used to select 7 studies of adult ALL that prospectively assessed overall survival (OS) using natural randomization based on donor availability combined with intention-to-treat analyses. The authors then performed a metaanalysis to evaluate the role of allogeneic HSCT.

RESULTS. Seven studies that included 1274 patients were selected. A metaanalysis demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups (hazard ratio [HR], 1.29; 95% confidence interval [95% CI], 1.02-1.63 [$P = .037$]). When only high-risk patients were included in the analysis, the superiority of the survival advantage was even greater (HR, 1.42; 95% CI, 1.06-1.90 [$P = .019$]). A meta-regression analysis revealed that compliance with allogeneic HSCT showed a significant and positive correlation with survival (coefficient, 0.022; $P<.01$), suggesting that the greater the proportion of patients who actually received allogeneic HSCT, the better the survival of the donor group. No beneficial effects of autologous HSCT were observed.

CONCLUSIONS. The current findings demonstrated that allogeneic HSCT improves the outcome of adult patients with high-risk ALL. Although these analyses were based on abstracted data, the results indicated that allogeneic HSCT should be considered for such patients if a suitable donor is available. ***Cancer* 2006;106: 2657–63.** © *2006 American Cancer Society.*

KEYWORDS: acute lymphoblastic leukemia, hematopoietic stem cell transplantation, allogeneic transplantation, complete remission, metaanalysis.

Although the multiagent chemotherapies in current use induce complete remission (CR) for the majority of patients with acute lymphoblastic leukemia (ALL), the prognosis for adult patients with ALL remains unsatisfactory because of the high incidence of recurrence.[1–5] Among postremission therapies, it has been shown that allogeneic hematopoietic stem cell transplantation (HSCT) has a better antileukemic effect than conventional chemotherapy or autologous HSCT, but it also has been associated with higher treatment-related mortality. The overall survival (OS) advantage of allogeneic

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TABLE 1
Study Characteristics

Reference	Study Title	Country	Accrual Period	Age Range For Eligibility, Years	Proportion of Patients with High-Risk ALL, %	Treatment Modalities Compared with Allo
Sebban et al., 1994[8]	LALA87	France	1986-1991	15-40	37.4	Auto/Chemo
Takeuchi et al., 2002[1]	JALSG ALL93	Japan	1993-1997	15-40	49.6*	Chemo
Dombret et al., 2002[11]	LALA94	France	1994-2000	15-55	100	Auto
Thomas et al., 2004[12]	LALA94	Europe	1994-2002	15-55	100	Auto/Chemo
Hunault et al., 2004[13]	GOELAL02	France	1994-1998	15-50	100	Auto
Labar et al., 2004[14]	EORTC ALL-3	Europe	1986-1996	15-50	74.5	Auto/Chemo
Ribera et al.[15]	PETHEMA ALL-93	Spain	1993-2002	15-50	100	Auto/Chemo

ALL: acute lymphoblastic leukemia; Allo: allogeneic transplantation; Auto: autologous transplantation; Chemo: chemotherapy; LALA: Leucemie Aigue Lymphoblastique de l'Adulte; JALSG: Japan Adult Leukemia Study Group; GOELAL: Groupe Ouest-Est des Leucemies Aigues, Lymphoblastic trial; EORTC: European Organization for Research and Treatment of Cancer; PETHEMA: Programa de Estudio y Tratamiento de las Hemopatias Malignas.

* Because of definition overlap, intermediate-risk and high-risk patients were combined.

HSCT performed during the first CR (CR1) is not clear at this time, mainly because the comparison of allogeneic HSCT with chemotherapy or autologous HSCT is complicated because of baseline differences among patient characteristics in each treatment group.[6,7] To minimize these biases, natural randomization by donor availability and intention-to-treat analysis have been adopted. Several studies employing such methods have been reported for adult patients with ALL but with inconsistent results.[8–15] These inconsistencies may be accounted for by the limited number of patients enrolled in a single study, which is attributable mainly to the rarity of this disease in adults. Therefore, we performed a metaanalysis to provide more precise estimates of the clinical efficacy of allogeneic HSCT as postremission therapy for adult patients with ALL.

MATERIALS AND METHODS

Selection of Studies

Studies were eligible for inclusion in the metaanalysis if they met all of the following criteria: 1) they were published before October 2005 as an original article written in English, 2) they dealt with ALL patients, 3) they prospectively offered allogeneic HSCT to all patients in CR1 with a suitable donor and offered chemotherapy or autologous HSCT to all others, 4) they provided data for an intention-to-treat analysis based on donor availability, and 5) they assessed outcomes in terms of OS. We chose OS as the outcome of interest because a comparison of disease-free survival may overestimate the effect of allogeneic HSCT. Studies that focused exclusively on children were excluded. When multiple reports were published from a single trial, the most suitable report for the purpose of this study was selected for inclusion. The initial literature search was conducted through MEDLINE by using the free text search terms *acute lympho* leukemia* OR *acute lympho* leukaemia* AND *transplant** AND *survival* AND *related* OR *sibling* OR *family donor* for articles that were published in English before October 2005. The search yielded 347 articles, 197 of which were excluded by screening their titles. The abstracts of the remaining 150 articles were reviewed, and 13 articles were retrieved in full for further consideration.[8–20] To reach a final decision on which articles to include in the analysis, we examined all candidate articles in detail and excluded another 6 articles,[9,16–20] because 1) a more suitable article[8] was available based on the same study ($n = 1$ article),[16] 2) the analysis was performed retrospectively ($n = 2$ articles),[17,20] 3) no comparison was made according to donor availability ($n = 1$ article),[19] 4) no intention-to-treat analysis was performed ($n = 1$ article),[18] and 5) data about OS could not be obtained ($n = 1$ article).[9] Finally, seven studies were selected for the current metaanalysis (Table 1).[8,10–15] All potentially relevant articles were reviewed by 3 independent investigators (M.Y., K.M., and T.S.).

Data Abstraction

To avoid errors in the data abstraction process, 3 reviewers (M.Y., K.M., and T.S.) independently abstracted data from the articles and subsequently compared the results. All data were checked for internal consistency, and disagreements were resolved by discussion. Characteristics that were abstracted from the articles included the name of the first author, year of publication, accrual period, study location, study name, number of patients, age criteria for study entry, proportion of high-risk patients, alternative treatment modalities to allogeneic HSCT, compliance with allogeneic HSCT, median duration from CR to allogeneic HSCT, proportion of patients who received autologous HSCT in the no-donor group, and hazard ratios (HRs)

TABLE 2
Study Results

Reference	No. of Patients (%)					Median Interval Between CR and Allo (Months)	HR (95% CI)	
	Eligible for Assignment	Donor Group	No-Donor Group	Donor Group Allo Recipients	No-Donor Group Auto Recipients		OS for All Patients	OS for High-Risk Patients*
Sebban et al., 1994[8]	257	116	141	92 (79.3)	40 (28.4)	2.1	1.24 (0.91-1.70)	1.38 (0.84-2.27)
Takeuchi et al., 2002[10]	142	34	108	24 (70.6)	10 (9.3)	6.8	1.17 (0.69-1.98)	1.30 (0.64-2.65)
Dombret et al., 2002[11]	103	60	43	51 (85.0)	23 (53.5)	Related, 3.8; unrelated, 4.6	1.71 (1.09-2.68)	1.71 (1.09-2.68)
Thomas et al., 2004[12]	259	100	159	96 (96.0)	89 (56.0)	2.3	1.49 (1.05-2.08)	1.49 (1.05-2.08)
Hunault et al., 2004[13]	147	41	106	39 (95.1)	86 (81.1)	3.0	2.70 (1.38-5.28)	2.70 (1.38-5.28)
Labar et al., 2004[14]	184	68	116	47 (69.1)	27 (23.3)	Not reported	0.98 (0.67-1.43)	Not assessed
Ribera et al., 2005[15]	182	84	98	57 (67.9)	32 (32.7)	Not reported	0.85 (0.58-1.24)	0.85 (0.58-1.24)

HR: hazard ratio; 95% CI: 95% confidence interval; Allo: allogeneic transplantation; Auto: autologous transplantation; CR: complete remission; OS: overall survival.

* HRs and 95% CIs for Takeuchi et al., Hunault et al., Thomas et al., and Ribera et al. were provided by the investigators; those for Dombret et al. and Labar et al. were abstracted from the literature; and those for Sebban et al. were calculated by using Kaplan–Meier survival curves according to the method of Parmar et al., 1998.[21] An HR >1.0 indicates that donor group survival was superior to survival in the no-donor group.

and 95% confidence intervals (95% CIs) for OS. When the data required for the analysis could not be abstracted from the literature, attempts were made to contact the investigators who conducted the studies.

Quantitative Data Synthesis

HRs were used to assess the impact of allogeneic HSCT on survival compared with alternative treatment modalities. The natural logarithm of a crude HR and its variance for each subcategory of the studies were calculated by using the abstracted survival probability at each time point with the methods proposed by Parmar et al.[21] and described elsewhere.[22] HRs were calculated to show how many times greater the probability of failure was for the donor group compared with the no-donor group, so that an HR greater than unity indicated that the survival rate for the donor group was superior to that for the no-donor group. A general variance-based method was used to estimate the summary HRs and their 95% CIs. We also calculated the interstudy variation (τ^2) from the Q statistic with the method described by DerSimonian and Laird.[23] Initially, both fixed-effect and random-effect models were used to calculate summary HRs; however, ultimately, only the random-effect model was used. Begg funnel plots[24] and Egger tests[25] were used to detect possible publication bias. Subgroup metaanalysis was used to assess the source of heterogeneity in the high-risk group. In addition, meta-regression analysis[26] was employed to detect the source of heterogeneity in survival analyses. The factors that were examined in the meta-regression analysis were initiation year, alternative treatment to allogeneic HSCT, proportion of patients in the donor group who actually received allogeneic HSCT, proportion of patients in the no-donor group who received autologous HSCT, and median duration from CR to allogeneic HSCT. There was no adjustment of multiple comparisons because of the lack of statistical power of the study and the inclusion of an a priori hypothesis.

All statistical analyses were conducted using Stata software (version 8; StataCorp, College Station, TX). We defined a P values $<.05$ as significant for summary HR.

RESULTS

Tables 1 and 2 summarize 7 studies eventually selected for inclusion in the metaanalysis.[8,10–15] Six studies were from Europe,[8,11–15] and 1 study was from Japan.[10] One study[14] covered not only patients with ALL but also patients with lymphoblastic lymphoma, who accounted for 12% of the patients. Two studies[8,14] were initiated in the late 1980s, and the rest[10-13,15] were initiated in the early 1990s. Four studies[8,12,14,15] had been designed to allocate either autologous HSCT or chemotherapy to patients in the no-donor groups. Only high-risk patients were included in 4 studies.[11–13,15] In 1 study that dealt only with Philadelphia chromosome (Ph)-positive ALL, the donor search was extended to matched unrelated donors.[11] The range of compliance with allogeneic HSCT in the donor group was from 67.9% to 96.0%, and the proportion of patients who actually received autologous HSCT in the no-donor group ranged from 9.3% to 81.1%.

The summary HR for OS was 1.29 (95% CI, 1.02-1.63 [$P = .037$]), as determined with the random-effect model, suggesting a significant survival advantage for the donor group (Table 3, Fig. 1). The heterogeneity test in the overall analysis showed a significant heter-

TABLE 3
Summary of Hazard Ratios and Proportional Weighting of Each Study in Relation to Overall Survival of the Entire Study Population

Reference	Compared Treatment Modalities	Weights of Each Study, %*
Sebban et al., 1994[8]	Auto/Chemo	18.3
Takeuchi et al., 2002[10]	Chemo	11.4
Dombret et al., 2002[11]	Auto	13.5
Thomas et al., 2004[12]	Auto/Chemo	16.8
Hunault et al., 2004[13]	Auto	8.4
Labar et al., 2004[14]	Auto/Chemo	15.8
Ribera et al., 2005[15]	Auto/Chemo	15.7
Summary		
HR†		1.29
95% CI		1.02-1.63
P		0.37

Auto: autologous transplantation; Chemo: chemotherapy; HR: hazard ratio; 95% CI: 95% confidence interval.

* Proportional weighting was converted to a percentage of total weighting in the random-effect model. The Q statistic was 13.1 with 6 degrees of freedom ($P = .037$), and interstudy variance (τ^2) was 0.054.

† An HR >1.0 indicates that survival in the donor group was superior to survival in the no-donor group.

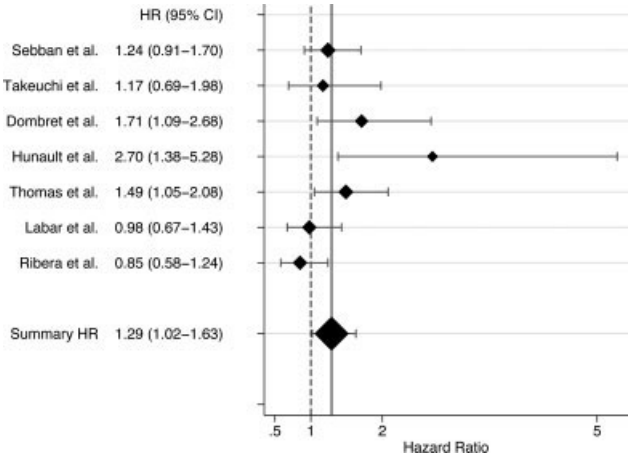

FIGURE 1. Forrest plots illustrate the hazard ratios (HR) and 95% confidence intervals (95% CI) for overall survival in the entire study population. The size of each diamond indicates the proportional weighting in the random-effect model of the metaanalysis. A HR greater than unity indicates that survival in the donor group was superior to survival in the no-donor group.

TABLE 4
Summary of Hazard Ratios and Proportional Weighting of Each Study in Relation to the Overall Survival of High-Risk Patients

Reference	Compared Treatment Modalities	Weights of Each Study, %*
Sebban et al., 1994[8]	Auto/Chemo	16.6
Takeuchi et al., 2002[10]	Chemo	11.1
Dombret et al., 2002[11]	Auto	18.1
Thomas et al., 2004[12]	Auto/Chemo	21.8
Hunault et al., 2004[13]	Auto	11.9
Ribera et al., 2005[15]	Auto/Chemo	20.6
Summary		
HR†		1.42
95% CI		1.06-1.90
P		.000

Auto: autologous transplantation; Chemo: chemotherapy; HR: hazard ratio; 95% CI: 95% confidence interval.

* Proportional weighting was converted to a percentage of total weighting in the random-effect model. The Q statistic was 11.1 with 5 degrees of freedom ($P = .049$), and interstudy variance (τ^2) was 0.071.

† An HR >1.0 indicates that survival in the donor group was superior to survival in the no-donor group.

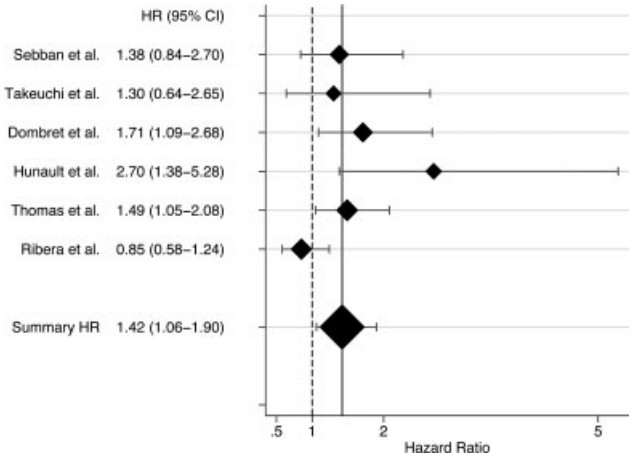

FIGURE 2. Forrest plots illustrate the hazard ratios (HR) and 95% confidence intervals (95% CI) for overall survival in patients with high-risk acute lymphoblastic leukemia. The size of each diamond indicates the proportional weighting in the random-effect model of the metaanalysis. A HR greater than unity indicates that survival in the donor group was superior to survival in the no-donor group.

ogeneity ($Q = 13.4$; degrees of freedom = 6; $P = .037$; $\tau^2 = 0.054$). When the analysis was restricted to patients with high-risk disease, the summary HR for OS increased to 1.42 (95% CI, 1.06-1.90; $P = .019$), indicating a greater benefit from allogeneic HSCT for this subset (Table 4, Fig. 2).

Table 5 illustrates the results from the univariate meta-regression analysis. Compliance with allogeneic HSCT showed a significant and positive correlation with survival (coefficient, 0.022; $P<.01$), indicating that the higher the compliance, the greater the benefit for the donor group. It is noteworthy that there was a significant and positive correlation with the proportion of autologous HSCT in the no-donor group (coefficient, 0.013; $P<.01$). This suggests a possibly adverse effect of autologous HSCT compared with chemotherapy as an alternative treatment to allogeneic HSCT. The negative correlation for chemotherapy (coefficient, − 0.562) and the positive correlation for autologous HSCT (coefficient, 0.112) support this hypothesis. Although it was not significant, the negative correlation (coefficient, − 0.030) for the median time

TABLE 5
Heterogeneity Determined by Univariate Meta-Regression Analysis

Source of Heterogeneity	Coefficient*	SE	*P*	Constant
Year in which trial was initiated	0.037	0.035	.29	−72.532
Treatment for no-donor group				
Auto (yes vs. no)	0.112	0.400	.78	0.157
Chemotherapy (yes vs. no)	−0.562	0.234	.02	0.689
Percentage of donor group patients who actually received Allo	0.022	0.007	<.01	−1.567
Percentage of no-donor group patients who actually received Auto	0.013	0.004	<.01	−0.250
Median interval between CR and Allo	−0.030	0.081	.71	0.500

SE indicates standard error; Auto, autologous transplantation; Allo, allogeneic transplantation; CR, complete remission.
* Coefficient in meta-regression analysis denotes the extent to which the presence of a given factor or an increase of 1 degree changes the hazard ratio established in the overall analysis by metaanalysis.

TABLE 6
Definitions of High-Risk Acute Lymphoblastic Leukemia

Reference	Definitions
Sebban et al., 1994[8]	Any patient with Ph or AUL; common ALL patients with age >35 y, WBC >30,000/μL, or time to CR >4 wk
Takeuchi et al., 2002[10]*	Any patient with Ph, age >30 y or WBC >30,000/μL
Dombret et al., 2002[11]†	Any patient with Ph
Thomas et al., 2004[12]	Any patient with CNS disease at diagnosis or who failed to achieve CR after the first induction course; B-lineage ALL patients with 11q23 rearrangements, t(1;19), WBC >30,000/μL, or myeloid markers
Hunault et al., 2004[13]	Any patient with poor-risk cytogenetics [Ph, t(4;11), t(1;19)], age >35 y, WBC >30,000/μL, or failure to achieve CR after the first induction course
Ribera et al., 2005[15]	Any patient with Ph, 11q23 rearrangements, t(1;19), age >30 y, or WBC >25,000/μL

Ph: Philadelphia chromosome; AUL: acute undifferentiated leukemia; ALL: acute lymphoblastic leukemia; WBC: white blood cell count; CR: complete remission; CNS: central nervous system.
* Because of definition overlap, intermediate-risk and high-risk patients were combined.
† Patients with Ph-positive ALL were treated on a different protocol.

until allogeneic HSCT suggests that a shorter interval between CR and allogeneic HSCT may enhance its beneficial effect.

DISCUSSION

Because the high incidence of recurrence is a main cause of treatment failure in adult patients with ALL, optimal postremission therapy is a matter of vital concern. In particular, the clinical efficacy of allogeneic HSCT is a critical issue, although the results from various studies that compared allogeneic HSCT with other modalities produced conflicting results, most likely because of several factors, including difficulties with the study design and the limited numbers of patients.[8–15] For the study design, it is accepted currently that natural randomization by donor availability can be substituted for true randomization and that analyzing the results on the basis of the intention-to-treat principle can minimize biases. Although these methods are considered valid, the main problem of this approach is diminished statistical power, which may lead to an underestimation of the true effect of allogeneic HSCT. Metaanalysis is a useful statistical method for integrating the results of independent studies for a specified outcome. The combination of relevant studies increases statistical power and makes it possible to detect effects that may be missed by individual studies. For this study, to assess the efficacy of allogeneic HSCT for adult ALL, we applied strict criteria in the selection of 7 studies,[8–15] all of which employed both natural randomization by donor availability and intention-to-treat analysis. These studies were then subjected to metaanalysis, which demonstrated that patients in the donor groups had significantly better survival than patients in the no-donor groups (HR, 1.29; 95% CI, 1.02-1.63 [$P = .037$]). When only high-risk patients were considered, the superiority of the survival advantage was even greater (HR, 1.42; 95%CI, 1.06-1.90 [$P = .019$]). Although it should be noted that the studies did not agree entirely on the definition of high-risk ALL (Table 6), they did not differ significantly, because the definitions comprised known risk factors, such as patient age, initial leukocyte counts, number of induction courses required to achieve CR, and the presence or absence of Ph. Our findings promote the concept that allogeneic HSCT is

the treatment of choice for patients with high-risk ALL, especially if they have a human leukemic antigen-identical sibling donor. Conversely, the efficacy of allogeneic HSCT for patients with standard-risk ALL remains uncertain, even after the current metaanalysis. This difficulty stems from the findings that 4 studies[11-13,15] included only high-risk patients and that data for standard-risk patients could not be obtained from 2 other studies.[8,14] The large prospective trial conducted by the Medical Research Council and the European Cooperative Oncology Group is expected to shed light on the efficacy of allogeneic HSCT for patients with standard-risk ALL.[27]

The current meta-regression analysis revealed several intriguing findings. Greater compliance with allogeneic HSCT increased its beneficial effect, confirming the therapeutic potential of the procedure. Because the duration of CR until allogeneic HSCT showed a negative correlation with survival, although it was not statistically significant, it can be assumed that allogeneic HSCT should be performed soon after CR has been attained. An unexpected finding was that a higher proportion of autologous HSCT in the no-donor groups enhanced the survival advantage of the donor groups. The reported results of autologous HSCT for adults with ALL generally have been disappointing[28] in contrast to the results for adults with acute myeloid leukemia,[29] with recurrence the most common cause of failure. No beneficial effects of autologous HSCT were observed in our study. However, this finding should be interpreted with caution, because the observation was based on the percentage of patients who actually received autologous HSCT, and stem cell purging was performed in some studies but not in others.

The results of the current metaanalysis demonstrated that allogeneic HSCT improves survival for patients with high-risk ALL. Because this study was based on abstracted data, the subsets of patients who benefited most (i.e., Ph-positive ALL) could not be determined, and a metaanalysis based on individual data is required. Despite such limitations, our results clearly indicate that allogeneic HSCT should be considered for patients with high-risk ALL if a suitable donor is available.

REFERENCES

1. Hoelzer D, Thiel E, Loffler H, et al. Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. *Blood.* 1988;71:123-131.
2. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: Cancer and Leukemia Group B study 8811. *Blood.* 1995;85:2025-2037.
3. Durrant IJ, Prentice HG, Richards SM. Intensification of treatment for adults with acute lymphoblastic leukaemia: results of U.K. Medical Research Council randomized trial UKALL XA. Medical Research Council Working Party on Leukaemia in Adults. *Br J Haematol.* 1997;99:84-92.
4. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol.* 2000;18:547-561.
5. Annino L, Vegna ML, Camera A, et al. Treatment of adult acute lymphoblastic leukemia (ALL): long-term follow-up of the GIMEMA ALL 0288 randomized study. *Blood.* 2002;99:863-871.
6. Wheatley K. Current controversies: which patients with acute myeloid leukaemia should receive a bone marrow transplantation?—a statistician's view. *Br J Haematol.* 2002;118:351-356.
7. Yanada M, Matsuo K, Emi N, Naoe T. Efficacy of allogeneic hematopoietic stem cell transplantation depends on cytogenetic risk for acute myeloid leukemia in first disease remission: a metaanalysis. *Cancer.* 2005;103:1652-1658.
8. Sebban C, Lepage E, Vernant JP, et al. Allogeneic bone marrow transplantation in adult acute lymphoblastic leukemia in first complete remission: a comparative study. French Group of Therapy of Adult Acute Lymphoblastic Leukemia. *J Clin Oncol.* 1994;12:2580-2587.
9. Attal M, Blaise D, Marit G, et al. Consolidation treatment of adult acute lymphoblastic leukemia: a prospective, randomized trial comparing allogeneic versus autologous bone marrow transplantation and testing the impact of recombinant interleukin-2 after autologous bone marrow transplantation. BGMT Group. *Blood.* 1995;86:1619-1628.
10. Takeuchi J, Kyo T, Naito K, et al. Induction therapy by frequent administration of doxorubicin with four other drugs, followed by intensive consolidation and maintenance therapy for adult acute lymphoblastic leukemia: the JALSG-ALL93 study. *Leukemia.* 2002;16:1259-1266.
11. Dombret H, Gabert J, Boiron JM, et al. Outcome of treatment in adults with Philadelphia chromosome-positive acute lymphoblastic leukemia—results of the prospective multicenter LALA-94 trial. *Blood.* 2002;100:2357-2366.
12. Thomas X, Boiron JM, Huguet F, et al. Outcome of treatment in adults with acute lymphoblastic leukemia: analysis of the LALA-94 trial. *J Clin Oncol.* 2004;22:4075-4086.
13. Hunault M, Harousseau JL, Delain M, et al. Better outcome of adult acute lymphoblastic leukemia after early genoidentical allogeneic bone marrow transplantation (BMT) than after late high-dose therapy and autologous BMT: a GOELAMS trial. *Blood.* 2004;104:3028-3037.
14. Labar B, Suciu S, Zittoun R, et al. Allogeneic stem cell transplantation in acute lymphoblastic leukemia and non-Hodgkin's lymphoma for patients < or = 50 years old in first complete remission: results of the EORTC ALL-3 trial. *Haematologica.* 2004;89:809-817.
15. Ribera JM, Oriol A, Bethencourt C, et al. Comparison of intensive chemotherapy, allogeneic or autologous stem cell transplantation as post-remission treatment for adult patients with high-risk acute lymphoblastic leukemia. Results of the PETHEMA ALL-93 trial. *Haematologica.* 2005;90:1346-1356.
16. Fiere D, Lepage E, Sebban C, et al. Adult acute lymphoblastic leukemia: a multicentric randomized trial testing bone marrow transplantation as postremission therapy. The French Group on Therapy for Adult Acute Lymphoblastic Leukemia. *J Clin Oncol.* 1993;11:1990-2001.

17. De Witte T, Awwad B, Boezeman J, et al. Role of allogenic bone marrow transplantation in adolescent or adult patients with acute lymphoblastic leukaemia or lymphoblastic lymphoma in first remission. *Bone Marrow Transplant.* 1994;14: 767-774.
18. Dekker AW, van't Veer MB, Sizoo W, et al. Intensive postremission chemotherapy without maintenance therapy in adults with acute lymphoblastic leukemia. Dutch Hemato-Oncology Research Group. *J Clin Oncol.* 1997;15:476-482.
19. Ifrah N, Witz F, Jouet JP, et al. Intensive short term therapy with granulocyte-macrophage-colony stimulating factor support, similar to therapy for acute myeloblastic leukemia, does not improve overall results for adults with acute lymphoblastic leukemia. GOELAMS Group. *Cancer.* 1999;86: 1496-1505.
20. Gupta V, Yi QL, Brandwein J, et al. The role of allogeneic bone marrow transplantation in adult patients below the age of 55 years with acute lymphoblastic leukemia in first complete remission: a donor versus no donor comparison. *Bone Marrow Transplant.* 2004;33:397-404.
21. Parmar MK, Torri V, Stewart L. Extracting summary statistics to perform metaanalyses of the published literature for survival endpoints. *Stat Med.* 1998;17:2815-2834.
22. Hotta K, Matsuo K, Ueoka H, Kiura K, Tabata M, Tanimoto M. Metaanalysis of randomized clinical trials comparing cisplatin to carboplatin in patients with advanced non-small-cell lung cancer. *J Clin Oncol.* 2004;22:3852-3859.
23. DerSimonian R, Laird N. Metaanalysis in clinical trials. *Control Clin Trials.* 1986;7:177-188.
24. Begg CB, Mazumdar M. Operating characteristics of a rank correlation test for publication bias. *Biometrics.* 1994;50: 1088-1101.
25. Egger M, Davey Smith G, Schneider M, Minder C. Bias in metaanalysis detected by a simple, graphical test. *BMJ.* 1997; 315:629-634.
26. Sharp S. Metaanalysis regression. Stata Tech Bull. 1998;42: 16-24.
27. Rowe J, Richards S, Burnett A. Favorable results of allogeneic bone marrow transplantation (BMT) for adults with Philadelphia (Ph)-chromosome-negative acute lymphoblastic leukemia (ALL) in first complete remission (CR): results from the International ALL Trial (MRC UKALL XII/ECOG E2993) [abstract]. *Blood.* 2001;98(Suppl 1):2009.
28. Gorin NC. Autologous stem cell transplantation in acute lymphocytic leukemia. *Stem Cells.* 2002;20:3-10.
29. Nathan PC, Sung L, Crump M, Beyene J. Consolidation therapy with autologous bone marrow transplantation in adults with acute myeloid leukemia: a metaanalysis. *J Natl Cancer Inst.* 2004;96:38-45.