Original Article

Management of Adult Patients With Acute Lymphoblastic Leukemia in First Complete Remission

Systematic Review and Meta-Analysis

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BACKGROUND: The optimal postremission therapy in adults with acute lymphoblastic leukemia (ALL) is still a matter of debate. The objective of this study was to compare the various potential therapeutic options for patients who achieved first complete remission. **METHODS:** The authors conducted a systematic review and meta-analysis of randomized trials, including patients with standard-risk (SR) All and high-risk (HR) ALL who received first postremission therapy. Outcomes assessed were all-cause mortality (ACM), disease recurrence (relapse), and nonrelapse mortality (NRM). Relative risks (RRs) with 95% confidence intervals (CIs) were estimated and pooled. **RESULTS:** Overall, there was a significant reduction in ACM in the allogenic stem cell transplantation (alloSCT) arm (RR, 0.88; 95% CI, 0.8-0.97) compared with autologous stem cell transplantation (ASCT) or chemotherapy. Subgroup analyses revealed a similar pattern among SR patients (RR, 0.8; 95% CI, 0.68-0.94) but a nonsignificant advantage for alloSCT among HR patients (RR, 0.88; 95% CI, 0.76-1.01). There was an increase in NRM (RR, 2.99; 95% CI, 1.37-6.53) and a decrease in the relapse rate in the alloSCT arm (RR, 0.52; 95% CI, 0.33-0.83). There was no difference in ACM or the relapse rate between the ASCT and chemotherapy arms. **CONCLUSIONS:** Overall, alloSCT was superior to ASCT or chemotherapy for patients with ALL in first complete remission. The survival advantage was of greater statistical significance for patients with SR ALL than for patients with HR ALL. ***Cancer* 2010;116:3447–57.** © *2010 American Cancer Society.*

KEYWORDS: acute lymphoblastic leukemia, allogeneic transplantation, autologous stem cell transplantation, chemotherapy, first complete remission.

The treatment of adult patients with acute lymphoblastic leukemia (ALL) usually consists of a remission induction phase and consolidation/intensification phases followed by either hematopoietic stem cell transplantation (HSCT) or maintenance therapy. Currently, it is uncertain whether patients who achieve a first complete remission (CR1) should either receive intensive treatment with HSCT or continue with conventional chemotherapy.[1-3] By combining clinical, immunophenotypic, cytogenetic, and molecular data, patients can be classified into standard-risk (SR) and high-risk (HR) groups according to their prognostic scores.[1,4]

An American Society of Blood and Marrow Transplantation position statement and an evidence-based review suggested that HSCT yields outcomes similar to chemotherapy and is not recommended as first-choice therapy in CR1.[5] Two previous meta-analyses indicated that the survival of patients who underwent allogeneic HSCT (alloSCT) was superior to the survival of patients who received chemotherapy, mainly in the HR group of patients.[6,7] Recently, 2 large prospective trials demonstrated superior survival for alloSCT in SR patients and a nonsignificant advantage in HR patients.[8-10] Therefore, we conducted a systematic review and meta-analysis based on randomized and genetically randomized trials to assess which is the optimal postremission treatment for ALL patients in CR1.

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We thank the authors who responded to our letters and supplied additional data on their trials.

DOI: 10.1002/cncr.25136, **Received:** July 22, 2009; **Revised:** September 12, 2009; **Accepted:** November 3, 2009, **Published online** April 27, 2010 in Wiley InterScience (www.interscience.wiley.com)

MATERIALS AND METHODS

Data Sources

We conducted a comprehensive search strategy with no restriction on language or study years to identify both published and unpublished trials. Relevant trials were identified by searching the Cochrane Library, PubMed, LILACS, and CANCERLIT up to March 2009. We searched the following conference proceedings for relevant abstracts: the American Society of Hematology (from 2004), the American Society of Clinical Oncology (from 2000), the European Hematology Association (from 2001), the American Society of Bone Marrow Transplantation (from 2007), the European Group for Blood and Marrow Transplantation (from 2005), and conferences of Experimental Hematology (available at: http://www.iseh.org/i4a/pages/index.cfm accessed March 1, 2009). The following trial databases were searched for ongoing and unpublished trials: current controlled trials in the MetaRegister of controlled clinical trials (available at: http://www.controlled-trials.com/ accessed March 1, 2009) and the National Institutes of Health Clinical Trials Registry (available at: http://clinicaltrials.gov/ accessed March 1, 2009). The references from all identified studies were investigated to identify more trials. In addition, the first or corresponding author of each included trial was contacted for information regarding unpublished trials or complementary information on their own trial. The following search terms were used for Medical Subject Heading (MeSH) headings (mh) to identify publication type (pt): transplant AND (acute lymphoblastic leukemia OR acute lymphoblastic leukemia OR acute lymphoblastic leukemia [MeSH]) AND (prospective OR longitudinal OR cohort OR randomized controlled trial [pt] OR controlled clinical trial [pt] OR randomized controlled trials [mh] OR random allocation [mh] NOT [animals (mh) NOT human (mh)]).

Study Selection

We included trials that assessed adult patients aged >15 years with ALL in CR1, because this was the age chosen by the majority of the studies as inclusion criteria. We included randomized controlled trials and genetically randomized studies, which we defined by patient allocation to intervention on the basis of sibling donor availability.[11] Trials were included only once in the analysis using the most updated data. Interventions that were assessed included alloSCT, autologous stem cell transplantation (ASCT), or conventional chemotherapy.

Data Extraction

Two reviewers independently extracted data from included trials (R.R. and A.G.-G.). In case of any disagreement between the 2 reviewers, a third reviewer extracted the data (L.V.). When necessary, the authors of the trials were contacted for clarification and complementary information on their trials.

Risk of Bias Assessment

Although genetically randomized trials serve as an alternative platform for randomized controlled trials, they do carry a higher risk for bias. Because the different trial arms are not truly randomized, various characteristics may not be well balanced and carry a potential for bias. Thus, trials that fulfilled the review inclusion criteria were assessed for methodological quality by 2 reviewers (R.R. and A.G.-G.). Not reporting of any of the items was considered as high risk for bias. For "standard" randomized trials, we assessed the methods used for sequence generation, allocation sequence concealment, blinding, and exclusions from analysis by using standard methods as recommended in the Cochrane Handbook.[12]

For genetically randomized controlled trials, we based our assessment on previous recommendations.[11] First, we evaluated whether the trial was analyzed with intention-to-treat (ITT) methodology. ITT was defined as the number of randomized patients that were excluded from their allocated intervention group for outcome assessment and the number of the nonrandomized patients included (no sibling or unrelated alloSCT). This was done because an "as treated" analysis might introduce bias in favor of alloSCT in the process of patient selection. We considered any violation of ITT as the sole most important risk of bias domain for genetically randomized trials.

The second step was to assess the following domains[11]:

1) Timing of study entry for patients in the alloHSCT versus conventional chemotherapy or ASCT groups and comparative duration of follow-up: Earlier recruitment of patients into the "no donor" group might introduce bias in favor of alloSCT, because this enables more time for outcomes to occur in the "no donor" group.
2) Method of tissue typing: Because genetic randomization depends on the assessment of sibling matching, adequate human leukocyte antigen (HLA) typing and reporting must be ensured.

Table 1. Definitions of High-Risk Disease in Included Studies

Study	Chromosomal Abnormalities			WBC Count, $\times 10^9$/dL					
	t(9,22)	t(4,11)	t(1,19)	B-ALL: >30	T-ALL: >100	Pro B-ALL Immunophenotype	Attained CR >4 Weeks or >2 Induction Courses[a]	Age, y	CNS Involved
Cornelissen 2008[8]	+	+	+	+	+	+	+		
Goldstone 2008[9]	+			+	+			>35	
Ribera 2005[21]	+	+	+	+				>30	
Labar 2004[19]				+			+		
Thomas 2004[18]	+	+		+			+		+
Takeuchi 2002[17]	NR								
Sebban 1994[14]	+			+		+	+	>30	
Attal 1995[15]	NR								
Hunault 2004[20]	+	+	+	+		B-ALL		>35	
Vey 2006[22]	+	+	+						
Bernasconi 1992[13]	+			+		+	+	>35	

WBC indicates white blood cell; t, translocation; B-ALL, B-cell acute lymphoblastic leukemia; T-ALL, T-cell acute lymphoblastic leukemia; CR, complete remission; CNS, central nervous system; +, positive; NR, not reported.
[a] From the start of induction.

3) Compliance with the assigned intervention: Poor compliance (eg, no alloSCT for patients with available sibling donors and unrelated alloSCT for patients without sibling donors) probably would not introduce systematic bias,[11] but it might introduce a mild dilution of any treatment effect (benefit or harm of HSCT or chemotherapy).
4) Comparability of potential confounders: The comparability of the study groups was assessed based on the following confounders: age, patient's risk group (SR/HR according to study definitions), and performance status (Eastern Cooperative Oncology Group [ECOG] or as defined in study).

Outcomes

The primary outcome measure was all-cause mortality (ACM) at the longest available follow-up if <5 years. We chose this length of time because it is long enough to reflect both regimen-related toxicities and recurrence-related mortality.[5] Secondary outcomes included nonrelapse mortality (NRM) and relapse rate.

Data Synthesis and Analysis

Dichotomous data were analyzed by calculating the relative risk (RR) for each trial with the 95% confidence interval (CI). We used the Mantel-Haenszel random-effects model to pool RRs throughout the review because of expected heterogeneity between studies related to different distribution of disease risk characteristics. The random effects model is based on the assumption that different studies are not identical but follow some (usually normal) distribution. The pooled estimate refers to the center of intervention effects. The confidence intervals describe the uncertainty in the location of this mean.[12]

We used the original definitions of the trials for the SR and HR groups (Table 1). In addition, we performed subgroup analyses to assess the impact of ITT methodology on the main results.

The number of patients needed to be treated (NNT) was calculated as the inverse of pooled risk differences. Differences in confounders were assessed using the Student *t* test or as reported in the primary publication. For the randomized controlled trials, we graded allocation concealment and generation as adequate, unclear, or inadequate.[12]

Analyses were conducted using the Review Manager, version 5.0 (RevMan 5) computer program (2008; Nordic Cochrane Center/Cochrane Collaboration, Copenhagen, Denmark). Formulae for all meta-analysis methods are provided in the statistical algorithms of RevMan 5 (available at http://www.cc-ims.net/revman/ accessed March 1, 2009 and at http://www.cochrane-handbook.org accessed March 1, 2009).

RESULTS

The search yielded 659 potentially relevant trials, and 80 of those trials were considered for further investigation; however, 67 of the 80 studies were excluded for various reasons (Fig. 1). Thirteen trials (17 comparisons)

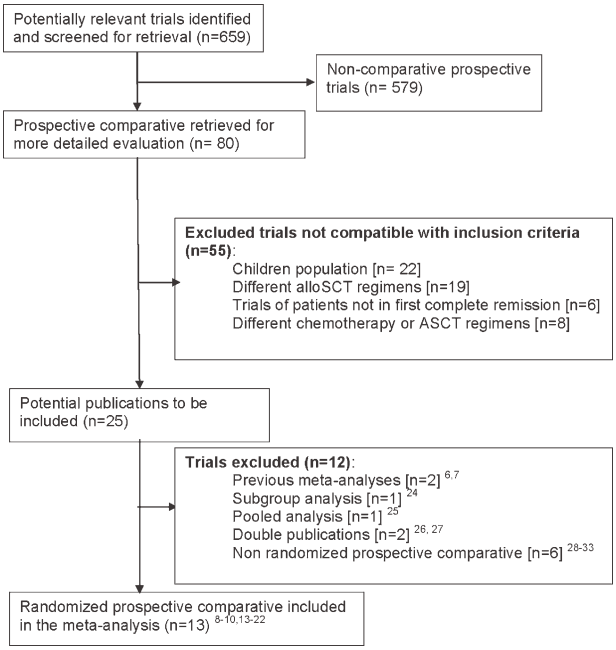

Figure 1. Trial flow according to (quality of reporting meta-analysis (QUOROM) is show. Superscript numerals cite the listed references. AlloSCT indicates allogeneic stem cell transplantation; ASCT, autologous stem cell transplantation.

conducted between 1986 and 2006 that randomized 2648 patients fulfilled inclusion criteria.[8-10,13-22] Two trials[15,22] did not report on mortality and were included only in the secondary outcome analysis. One trial compared ASCT with chemotherapy only.[16] Twelve trials compared alloSCT with other treatment modalities (10 trials compared alloSCT with ASCT or chemotherapy,[9,10,13-15,17,19-22] and 2 trials compared alloSCT with ASCT only[8,18]). Five trials (6 publications) compared ASCT with chemotherapy[9,13,16,18,19,21] (Table 2). It is noteworthy that 3 trials were updates of previously published studies and were included only once in the current analysis.[9,18,19]

Induction therapy for ALL included various regimens. The definition of HR patients was not consistent between trials (Table 1). All trials used myeloablative conditioning based on a total body irradiation (TBI)/cyclophosphamide regimen. The mean duration of follow-up among all studies was 62 months (range, 30-110 months). Data regarding demographics, host and donor characteristics, transplantation protocol, and post-transplantation data are summarized in Table 2.

Assessment of Risk of Bias

Twelve trials that compared alloSCT with other treatments were randomized genetically, and the analysis in 9 of those trials included an ITT desisgn.[9,10,13-15,17,18,21,22] Reasons for the inability to perform ITT analysis included the inclusion of patients who underwent matched unrelated donor transplantation in the nondonor study arm[8] and the inclusion of patients with no siblings in the nondonor arm.[19] In 1 study that had 2 arms, only 1 arm fulfilled the ITT definitions (ALL patients with central nervous system involvement).[18] The other arm (patients with Philadelphia chromosome-positive ALL) was considered non-ITT because it included patients who had matched unrelated donors and lacked sufficient clarity regarding the randomized numbers.

Most of the studies did not report data on potential cofounders (Table 3). The rate of compliance with the assigned intervention ranged between 56% and 95%. Trials that compared ASCT with chemotherapy used standard randomization; 2 of the 6 trials reported adequate randomization generation and allocation concealment. None of the trials were blinded (Table 3).

AlloSCT Versus Other Treatment Options

Primary outcome: ACM

There was a significant reduction in ACM in the alloSCT arm compared with the chemotherapy or ASCT arm (RR, 0.88; 95% CI, 0.8-0.97; 10 trials, 2600 patients) (Fig. 2, Top). We analyzed separately the trials that used or did not use an ITT design. When only trials that reported outcomes based on ITT analysis were included, there was a significant reduction in ACM with alloSCT (RR, 0.89; 95% CI, 0.82-0.97; 7 trials, 1863 patients) (Fig. 2, Top). Trials that did not report ITT analysis had a lower effect estimate without statistical significance (RR, 0.8; 95% CI, 0.64-1.02; 4 trials). Heterogeneity was demonstrated only in the non-ITT analyses. The NNT to prevent 1 death with alloSCT for the ITT trials was 17 (95% CI, 9-50), and the unadjusted mortality rate was 57% in the control group. An analysis that was conducted after exclusion of the Medical Research Council (MRC)/ECOG trial (which contributed 38% of the patients) yielded an RR similar to that obtained for the overall mortality, although the difference was not statistically significant (RR, 0.89; 95% CI, 0.78-1.02; percentage of variability caused by heterogeneity [I^2], 40%; 9 trials).

Two trials, neither of which used ITT methodology, compared alloSCT with ASCT and did not report a statistically significant difference between the 2 arms (RR, 0.66; 95% CI, 0.34-1.26; I^2, 76%; 2 trials).[8,20] Only 1 trial that used ITT methodology compared alloSCT with

Table 2. Characteristics of Included Studies

Study and Comparison Arms	No. Randomized: Arm 1/Arm 2	Age: Mean±SD or Median [Range], y	High-Risk Patients, %	Donor Type (No. of Patients)	Stem Cell Source	Conditioning Regimen	Follow-Up Duration: Mean [Range], mo
Bernasconi 1992[13]							36
AlloSCT/other	16/29	NR	NR	MRD	BMT	NR	
ASCT/chemotherapy	14/15	NR	NR	NA	NA	NR	
Sebban 1994[14]							
AlloSCT/other	116/141	26/24	35/39	MRD	BMT	Cy, TBI	62
Attal 1995[15]							
AlloSCT/other	43/77	31	20	MRD	BMT	Cy, TBI	30
Thiebaut 2000[16]							
ASCT/chemotherapy	58/59	24	39	NA	NA	Cy, TBI, and purging	120
Takeuchi 2002[17]							
AlloSCT/chemotherapy	34/108	NR	NR	MRD	PSCT	NR	63
Thomas 2004[18]		33 [15-55]	100		PSCT	Cy, TBI	64
AlloSCT/ASCT	93/95			MRD (65), MUD (10)			
ASCT/chemotherapy	70/59			NA			
Labar 2004[19]					NR	Cy, TBI	110
AlloSCT/other	68/116	29.5 [14-48]	72	MRD			
ASCT/chemotherapy	24/21	26 [14-50]	76	NA			
Hunault 2004[20]							61
AlloSCT/other	41/115	NR	100	MRD	BMT	Cy, TBI, and VP16	
Ribera 2005[21]					PSCT+BMT	Cy, TBI	70
AlloSCT/other	84/98	29 [16-49]	100	MRD			
ASCT/chemotherapy	50/48	25 [15-50]/27 [15-50]		NA			
Vey 2006[22]							
AlloSCT/other	16/29	31 [7-49]	100	MRD	PSCT	Cy, TBI	64
Goldstone 2008[9]		NR			NR	NR	59
AlloSCT/other	443/588		46/45	MRD			
ASCT/chemotherapy	229/227		56/55				
Cornelissen 2009[8]							
AlloSCT/ASCT	96/161	31/26	48/45	MRD, MUD	NR	Cy, TBI/Bu, Cy	65
Fielding 2009[10]							
AlloSCT/other	81	40 [15-60]	100	MRD (45), MUD (31)	NR	VP16, TBI	98 [38-171]

SD indicates standard deviation; AlloSCT, allogeneic stem cells transplantation; NR, not reported; MRD, matched related donor; BMT, bone marrow transplantation; ASCT, autologous stem cells transplantation; NA, not applicable; Cy, cyclophosphamide; TBI, total body irradiation; PSCT, peripheral blood stem cell transplantation; VP16, etoposide; PSCT, peripheral stem cell transplantation; MUD, matched unrelated donor; Bu, busulfan.

Table 3. Risk of Bias Assessment According to the Comparison of Variables Between Study Arms[a]

	ITT Evaluation						Potential Confounders Evaluation			
Study Group and Reference	Met ITT Criteria	No. Randomized	No. Evaluated	No. Actually Received Treatment (%)	Entry/ Follow-Up Duration	Tissue Typing	Compliance, %	Age	Risk Group	PS	Allocation Generation/ Concealment
Exclusively GRS											NA
Sebban 1994[14]	Yes	116/141	116/141	92/117 (79/83)	NR	NR	79	*P*=NS between arms	*P*=NS between arms	NR	
Attal 1995[15]	Yes	43/77	43/77	41/64 (95/83)	NR	NR	95	NR	NR	NR	
Takeuchi 2002[17]	Yes	34/108	34/108	24/81 (71/75)	NR	NR	71	NR	NR	NR	
Fielding 2009[10]	Yes	81/77	81/77	45/44 (56/57)	NR	High resolution	56	NR	All HR	NR	
Hunault 2004[20]	No	41/115	41/115	39/86 (95/75)	NR	NR	95	NR	All HR	NR	
Vey 2006[22]	Yes	20/27	20/27	NR	NR	NR	NR	NR	All HR	NR	
Cornelissen 2009[8]	No	96/161	96/161	91/123 (95/76)	Equal follow-up	High resolution	95	*P*=.01	*P*=NS between arms	NR	
GRS with RCT arm											
Bernasconi 1992[13]	Yes	16/29	16/29	11/25 (69/86)	NR	NR	69	NR	NR	NR	B/B
Thomas 2004[18]	Yes[b]	93/95	93/95	NR	NR	NR	NR	NR	All HR	NR	B/B
Labar 2004[19]	No	68/116	68/116	47/104 (69/90)	NR	NR	69	*P*=NS between arms	*P*=NS between arms	NR	A/A
Ribera 2005[21]	Yes	84/98	84/98	57/67 (68/68)	NR	NR	68	NR	All HR	NR	B/B
Goldstone 2008[9]	Yes	443/588	443/588	310/539 (70/92)	NR	High resolution	70	NR	*P*=NS between arms	NR	B/B
Exclusively RCT											
Thiebaut 2000[16]	Yes	95/96	95/96	NR	NA	NA	NA	NA	NA	NA	B/B

ITT indicates intention to treat; PS, performance status; GRS, genetically randomized studies; RCT, randomized controlled trial; NR, not reported; NS, not significant; NA, not applicable; HR, high risk; B, unclear; A, adequate; NR, not reported.

[a] GRS assessed for the following categories: high-risk bias, ITT, follow-up duration, tissue typing, compliance, age, risk group, and performance status (see Materials and Methods).

[b] Only for Group 4; Group 3 did not meet criteria for ITT analysis.

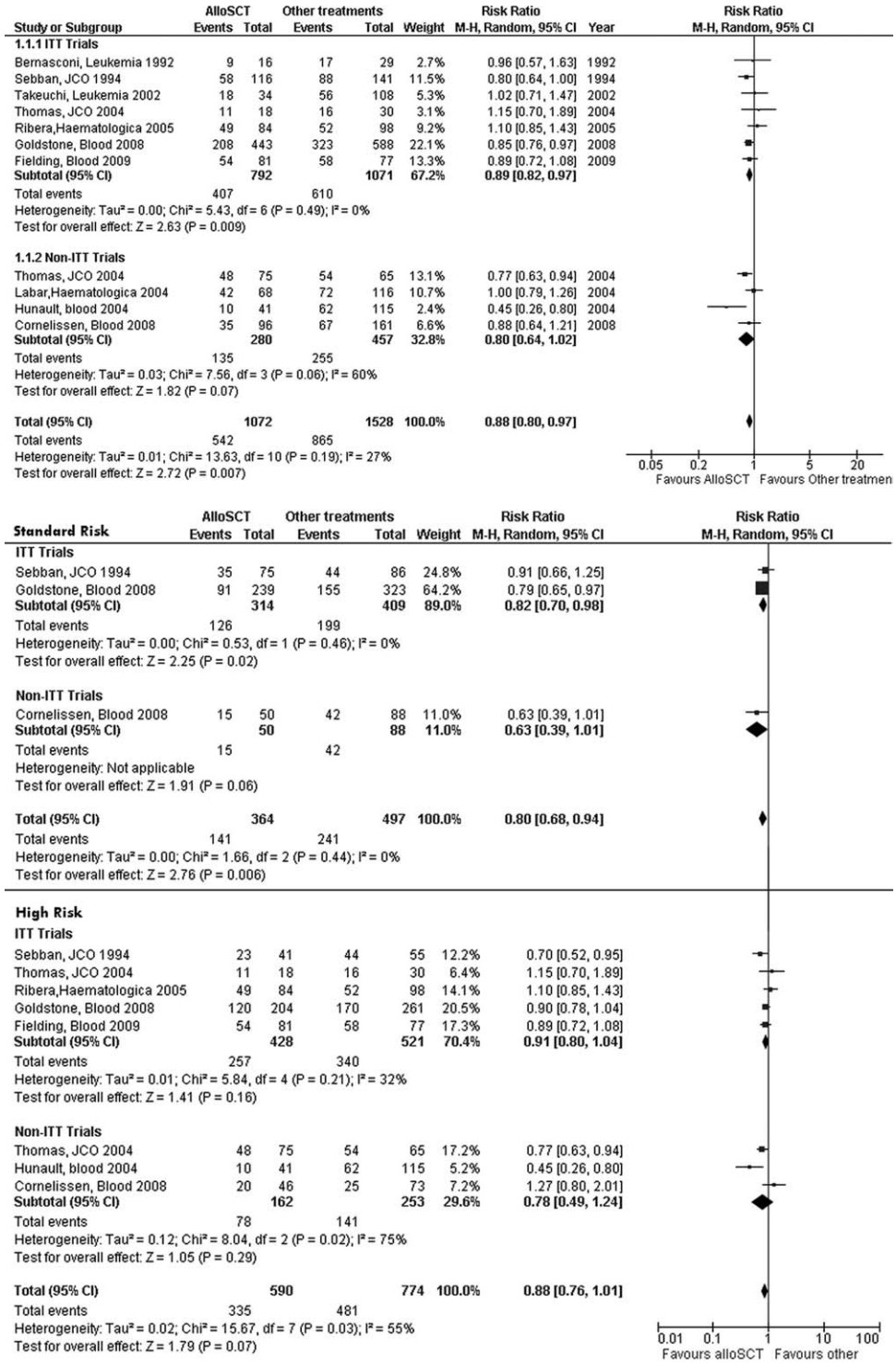

Figure 2. All-cause mortality for the comparison of allogeneic stem cell transplantation (alloSCT) versus autologous stem cell transplantation (ASCT)/chemotherapy is shown (*Top*) for the entire group of patients and (*Bottom*) in a subgroup analysis of standard-risk and high-risk patients. Sensitivity analysis was based on intention-to-treat (ITT) methodology. Relative risks were pooled using the random-effects model on a logarithmic scale from 0.1 to 10. M-H indicates Mantel-Haenszel; CI, confidence interval; JCO, *Journal of Clinical Oncology*; df, degrees of freedom.

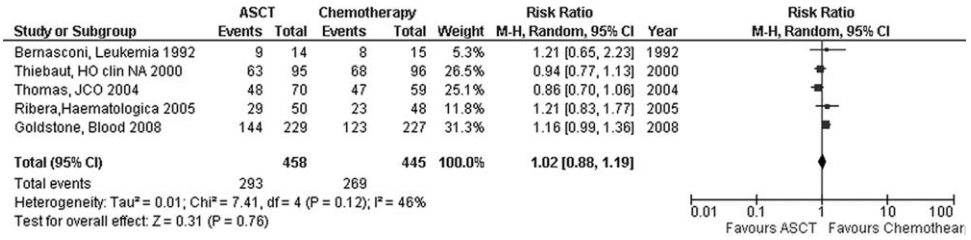

Figure 3. All-cause mortality for the comparison of autologous stem cell transplantation (ASCT) versus chemotherapy is shown. Relative risks were pooled using the random-effects model on a logarithmic scale from 0.1 to 10. M-H indicates Mantel-Haenszel; CI, confidence interval; HO Clin NA, *Hematology/Oncology Clinics of North America*; JCO, *Journal of Clinical Oncology*.

chemotherapy and did not report a statistically significant difference between the 2 arms (RR, 1.02; 95% CI, 0.71-1.47; 1 trial).[17]

ACM for SR patients

Three trials that randomized 861 patients reported on ACM for SR patients.[8,9,14] There was a significant reduction in ACM in the alloSCT arm (RR, 0.80; 95% CI, 0.68-0.94; 3 trials) (Fig. 2, Bottom). Sensitivity analysis for the ITT trials only produced similar results, ie, a significant reduction in ACM in the alloSCT arm (RR, 0.82; 95% CI, 0.7-0.98; 2 trials). No heterogeneity was demonstrated. The NNT for the ITT trials was 11 (95% CI, 6-100), and the control event rate was 49%.

ACM for HR patients

Seven trials that randomized 1364 patients reported on ACM for HR patients.[8-10,14,18,20,21] Although the RR was similar to that obtained for overall mortality, it was not statistically significant (RR, 0.88; 95% CI, 0.76-1.01; I^2, 55%; 7 trials) (Fig. 2, Bottom). Sensitivity analysis indicated a higher RR for the ITT studies (RR, 0.91; 95% CI, 0.8-1.04; I^2, 32%; 5 trials) than the non-ITT studies (RR, 0.78; 95% CI, 0.49-1.01; I^2, 75%; 3 trials) with overlapping 95% CIs. An analysis that was conducted after exclusion of the MRC/ECOG trial (which contributed 38% of the patients) yielded an RR similar to that obtained for overall mortality in HR patients (RR, 0.87; 95% CI, 0.68-1.11; I^2, 67%; 6 trials).

Secondary outcomes

There was a significant increase in NRM in the alloSCT arm (RR, 2.99; 95% CI, 1.37-6.53; I^2, 74%; 5 trials, 1746 patients). Sensitivity analysis of the ITT trials indicated a similar increase without statistical significance (RR, 2.07; 95% CI, 0.69-6.2; I^2, 82%; 3 trials).

There was a significant reduction in the recurrence rate in the alloSCT arm (RR, 0.52; 95% CI, 0.33-0.83; I^2, 86%; 6 trials, 1156 patients). A sensitivity analysis of the ITT studies produced similar results without statistical significance (RR, 0.58; 95% CI, 0.25-1.33; I^2, 92%; 3 trials). Both secondary outcomes demonstrated significant heterogeneity, possibly because some trials included only HR patients,[20,21] whereas others included both HR and SR patients.[8,9,15]

ASCT Versus Chemotherapy

Five conventionally randomized trials (6 publications) that enrolled 963 patients compared ASCT with chemotherapy.[9,13,16,18,19,21] The results of 1 of those studies[16] also were reported in another article.[19]

There was no difference in ACM between the ASCT and chemotherapy arms (RR, 1.02; 95%CI, 0.88-1.19; I^2, 46%; 5 trials, 903 patients) (Fig. 3). Similarly, there was no difference in ACM in a subgroup analysis of the SR group (RR, 1.03; 95% CI, 0.72-1.47; I^2, 64%; 2 trials) and the HR group (RR, 1.03; 95% CI, 0.91-1.17; 4 trials).

There was a significant increase in NRM in the ASCT arm compared with the chemotherapy arm (RR, 1.77; 95% CI, 1.12-2.8; 2 trials). There was no difference in the recurrence rate between the 2 arms (RR, 0.92; 95% CI, 0.73-1.15; I^2, 74%; 3 trials).

DISCUSSION

It is well accepted that postremission recurrence is the main cause of death in adult patients with ALL. Therefore, patients should receive further treatment with alloSCT, ASCT, or conventional chemotherapy. The objective of our current systematic review was to identify the optimal postremission therapy for adult patients with ALL in first CR. We included 13 randomized or genetically randomized trials that enrolled 2648 patients and compared alloSCT, ASCT, and conventional chemotherapy.

We observed a significant reduction in ACM in the alloSCT arm versus the ASCT or conventional chemotherapy arm for all patients (RR, 0.88; 95% CI, 0.8-0.97) that also was confirmed for SR patients as a group (RR, 0.80; 95% CI, 0.68-0.94; 861 patients). Although more patients were included in the HR group, the difference was not statistically significant for these patients (RR, 0.88; 95% CI, 0.76-1.01; 1364 patients). When only genetically randomized trials with ITT analysis were included, the results were similar between the SR group, the HR group, and all patients.

The interpretation of these results is that, overall, for ALL patients who achieved first CR, alloSCT had a survival benefit compared with the other options. The survival advantage for alloSCT had greater magnitude and statistical significance only for the SR patients. In this group, the validity of results was strengthened by the low heterogeneity and the narrow CI, although the results were derived from only 2 ITT trials and 1 non-ITT trial. The NNT to prevent 1 death with alloSCT for the SR group was 11 (95% CI, 6-100). This number, which reflects mortality risk reduction, supports the notion that alloSCT is superior to other treatments for patients with SR ALL. Conversely, the greater heterogeneity and the finding that the results were not significant make it hard to determine which treatment is best for patients with HR ALL.

Our results are in accordance with the findings of the recently published MRC/ECOG trial, which demonstrated that SR patients are the main group of ALL patients that may benefit from alloSCT.[9] When we excluded the results of that study from our meta-analysis (for all patients and for the HR group), the results remained similar, although they were not statistically significant. Contrary to a previous meta-analyses and to the common notion, we could not demonstrated that HR patients would benefit from alloSCT.[6,7] This difference may stem from 2 main causes: The first is the inclusion of 2 recent large trials, especially the MRC/ECOG trial,[8-10] which is considered the largest randomized trial to date and demonstrated a significant improvement in overall survival with alloSCT mainly for patients with SR ALL.[9] The second explanation stems from the methodology of our meta-analysis, in which we used different inclusion criteria for various studies in the meta-analysis, ie, we included only genetically randomized studies and put emphasis on studies that used an ITT methodology.

Our second comparison between ASCT and chemotherapy (5 trials, 963 patients) yielded similar ACM and recurrence rate results for both arms. There was no superiority for either arm in subgroup analysis according to risk group. However, there was a significant increase in NRM in the ASCT arm (RR, 1.77; 95% CI, 1.12-2.8). Physicians who care for these patients should take these data into consideration when recommending treatment for patients who are not eligible for alloSCT. Although it is only speculative, it is possible that certain patient groups (such as younger patients and those without significant comorbidities) may have lower NRM compared with conventional chemotherapy and, thus, may benefit from ASCT. Recently, phase 2 trials demonstrated that a pediatric-inspired intensive chemotherapy approach markedly improved the outcome of adult and adolescence patients with Philadelphia chromosome-negative ALL.[23] Therefore, the issue of whether ASCT and chemotherapy are equivalent still should be addressed in future studies.

There are several limitations to this systematic review. First, we could not conduct subgroup analyses according to specific HR features. Specifically, we could not conduct a subgroup analysis based on the age of patients because of the sparse data in many of the trials. Furthermore, there are several groups of patients for whom our conclusions may not be applicable. The first group includes patients with Philadelphia chromosome-positive ALL, because the role of incorporating tyrosine kinase inhibitors into treatment protocols has not yet been elucidated. The other group includes patients who undergo transplantation with reduced-intensity conditioning regimens. These procedures have become more popular in recent years, and their NRM and recurrence rates differ from those reported in the studies that we included in our current meta-analysis.

Another main limitation of our meta-analysis is the paucity of prospective randomized controlled trials. ALL is relatively uncommon in adults, and there is no optimal way to perform a randomized controlled trial. Although genetic randomization is a well accepted alternative,[11] it needs to be conducted appropriately according to strict methodological rules with adequate reporting. In our review, some trials did not report on ITT, and some did not evaluate the possible confounders between the 2 arms Furthermore, some of our analyses indicated statistical heterogeneity. This may be explained by different populations of patients, different percentages of patients that actually received the allocated treatment, and variable definitions of the risk groups. However, for the results that were statistically significant, most studies demonstrated a certain degree of benefit for the intervention rather than

divergent results. The diverse definitions of HR disease might have contributed to the significant heterogeneity in the subgroup analysis of the HR patient subgroup.

Implications for Practice and for Research

Our systematic review indicates an overall benefit from alloSCT for patients with ALL in first CR. The survival advantage is of greater magnitude and statistical significance for SR patients. For HR patients, ITT-based genetically randomized trials that will assess different HR features are needed to evaluate the best postremission treatment. The role of tyrosine kinase inhibitors, reduced intensity conditioning, and alternative donor alloSCT should be assessed in future trials.

Future trials should aim at reporting on ACM and should try to apply uniform risk criteria when reporting on outcomes of different subgroups. Attempts to minimize the risk of bias in these trials are crucial.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

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