



Effect of Postremission Therapy before Reduced-Intensity Conditioning Allogeneic Transplantation for Acute Myeloid Leukemia in First Complete Remission

Erica D. Warlick^{1,*}, Kristjan Paulson², Ruta Brazauskas³, Xiaobo Zhong³, Alan M. Miller⁴, Bruce M. Camitta⁵, Biju George⁶, Bipin N. Savani⁷, Celalettin Ustun¹, David I. Marks⁸, Edmund K. Waller⁹, Frédéric Baron¹⁰, César O. Freytes¹¹, Gérard Socie¹², Gorgun Akpek¹³, Harry C. Schouten¹⁴, Hillard M. Lazarus¹⁵, Edwin M. Horwitz¹⁶, John Koreth¹⁷, Jean-Yves Cahn¹⁸, Martin Bornhauser¹⁹, Matthew Seftel², Mitchell S. Cairo²⁰, Mary J. Laughlin²¹, Mitchell Sabloff²², Olle Ringdén²³, Robert Peter Gale²⁴, Rammurti T. Kamble²⁵, Ravi Vij²⁶, Usama Gergis²⁷, Vikram Mathews⁷, Wael Saber³, Yi-Bin Chen²⁸, Jane L. Liesveld²⁹, Corey S. Cutler¹⁷, Armin Ghobadi³⁰, Geoffrey L. Uy²⁴, Mary Eapen³, Daniel J. Weisdorf¹, Mark R. Litzow³¹

¹ Division of Hematology, Oncology, and Transplantation, University of Minnesota, Minneapolis, Minnesota

² University of Manitoba, Winnipeg, Manitoba, Canada

³ Center for International Blood and Marrow Transplant Research, Medical College of Wisconsin, Milwaukee, Wisconsin

⁴ Baylor University Medical Center, Dallas, Texas

⁵ Midwest Center for Cancer and Blood Disorders, Medical College of Wisconsin and Children's Hospital of Wisconsin, Milwaukee, Wisconsin

⁶ Christian Medical College Hospital, Vellore, India

⁷ Vanderbilt University Medical Center, Nashville, Tennessee

⁸ Bristol Adult BMT Unit, Bristol Children's Hospital, Bristol, United Kingdom

⁹ Bone Marrow and Stem Cell Transplant Center, Emory University Hospital, Atlanta, Georgia

¹⁰ Universitaire de Liege, Centre Hospitalier Universitaire - Sart-Tilman, Liege, Belgium

¹¹ South Texas Veterans Health Care System and University of Texas Health Science Center San Antonio, San Antonio, Texas

¹² Service d'Hématologie, Hôpital Saint Louis, Paris, France

¹³ Banner MD Anderson Cancer Center, Gilbert, Arizona

¹⁴ Academisch Ziekenhuis Maastricht, Maastricht, Netherlands

¹⁵ Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, Ohio

¹⁶ Children's Hospital of Philadelphia, Philadelphia, Pennsylvania

¹⁷ Dana Farber Cancer Institute, Boston, Massachusetts

¹⁸ Department of Hematology, University Hospital, Grenoble, France

¹⁹ Medizinische Klinik und Poliklinik I, Universitätsklinikum Carl Gustav Carus, Dresden, Germany

²⁰ Maria Fareri Children's Hospital, New York Medical College, Valhalla, New York

²¹ Hematopoietic Cell Transplantation Program, University of Virginia, Charlottesville, Virginia

²² Division of Hematology, Department of Medicine, University of Ottawa and The Ottawa Hospital Research Institute, Ottawa, Ontario, Canada

²³ Centre for Allogeneic Stem Cell Transplantation, Karolinska University Hospital, Stockholm, Sweden

²⁴ Section of Hematology, Division of Experimental Medicine, Department of Medicine, Imperial College, London, United Kingdom

²⁵ Center for Cell and Gene Therapy, Baylor College of Medicine, Houston, Texas

²⁶ Washington University School of Medicine, St. Louis, Missouri

²⁷ Weill Cornell Medical College, New York, New York

²⁸ Department of BMT, Massachusetts General Hospital, Boston, Massachusetts

²⁹ Strong Memorial Hospital, University of Rochester Medical Center, Rochester, New York

³⁰ Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, Texas

³¹ Hematology and Internal Medicine, Mayo Clinic Rochester, Rochester, Minnesota

Article history:

Received 19 August 2013

Accepted 28 October 2013

Key Words:

AML

RIC

Cytarabine consolidation

ABSTRACT

The impact of pretransplant (hematopoietic cell transplantation [HCT]) cytarabine consolidation therapy on post-HCT outcomes has yet to be evaluated after reduced-intensity or nonmyeloablative conditioning. We analyzed 604 adults with acute myeloid leukemia in first complete remission (CR1) reported to the Center for International Blood and Marrow Transplant Research who received a reduced-intensity or nonmyeloablative conditioning HCT from an HLA-identical sibling, HLA-matched unrelated donor, or umbilical cord blood donor from 2000 to 2010. We compared transplant outcomes based on exposure to cytarabine postremission consolidation. Three-year survival rates were 36% (95% confidence interval [CI], 29% to 43%) in the no consolidation arm and 42% (95% CI, 37% to 47%) in the cytarabine consolidation arm ($P = .16$). Disease-free survival was 34% (95% CI, 27% to 41%) and 41% (95% CI, 35% to 46%; $P = .15$), respectively. Three-year

Financial disclosure: See Acknowledgments on page 6.

E-mail address: ewarlick@umn.edu (E.D. Warlick).

* Correspondence and reprint requests: Erica D. Warlick, MD, Division of Hematology, Oncology and Transplantation, University of Minnesota, Mayo Mail Code 480, 420 Delaware Street SE, Minneapolis, MN 55455.

1083-8791/\$ – see front matter © 2013 American Society for Blood and Marrow Transplantation.

<http://dx.doi.org/10.1016/j.bbmt.2013.10.023>

cumulative incidences of relapse were 37% (95% CI, 30% to 44%) and 38% (95% CI, 33% to 43%), respectively ($P = .80$). Multivariate regression confirmed no effect of consolidation on relapse, disease-free survival, and survival. Before reduced-intensity or nonmyeloablative conditioning HCT, these data suggest pre-HCT consolidation cytarabine does not significantly alter outcomes and support prompt transition to transplant as soon as morphologic CR1 is attained. If HCT is delayed while identifying a donor, our data suggest that consolidation does not increase transplant treatment-related mortality and is reasonable if required.

© 2013 American Society for Blood and Marrow Transplantation.

INTRODUCTION

Decision-making regarding type of consolidation therapy after first complete remission (CR1) for acute myeloid leukemia (AML) depends on many patient- and disease-related variables. Postremission consolidation cytarabine chemotherapy can potentially cure a subset of AML patients, especially those with core binding factor leukemias [1–3]. However, a meta-analysis has suggested a survival benefit for a broader application of allografts for all intermediate and high risk AML patients in CR1, excluding only those with good risk cytogenetic or molecular features [4].

When an allograft is planned in a patient with AML in CR1, an abbreviated course of cytarabine consolidation therapy is often offered before hematopoietic cell transplantation (HCT) while a donor is being identified. Despite this common practice, the impact of pretransplant consolidation chemotherapy on post-HCT outcomes for AML CR1 patients has not been prospectively evaluated. This question has been retrospectively addressed by prior Center for International Blood and Marrow Transplant Research (CIBMTR) and European Group for Blood and Marrow Transplantation analyses with myeloablative (MA) conditioning. Pretransplant consolidation therapy did not alter survival or relapse and did not increase transplant-related mortality (TRM) [5,6]. The influence of pretransplant cytarabine consolidation chemotherapy in the setting of reduced-intensity conditioning (RIC)/non-MA (NMA) HCT for this patient population is uncertain. Prior retrospective analyses comparing outcomes after MA or RIC/NMA conditioning suggest a higher rate of relapse after RIC/NMA HCT but less TRM and thus similar survivals, even in older populations receiving RIC HCT [7–9]. These data would theoretically lead to the hypothesis that pre-HCT chemotherapy might reduce relapse risk after RIC all-HCT. Most recent retrospective and prospective publications, however, have challenged this earlier supposition, showing relatively similar relapse and TRM, regardless of conditioning intensity [10–13].

In the context of expanding use of RIC/NMA HCT, a setting where more stringent disease control may be desirable, the effectiveness of pre-HCT consolidation chemotherapy is largely unknown. A retrospective analysis from the University of Minnesota compared the outcomes of 60 AML patients in CR1 undergoing the same RIC HCT from 2001 to 2008 based on exposure to pre-HCT consolidation chemotherapy [14]. The investigators reported similar relapse and survival in subjects who did or did not receive pre-HCT consolidation [14]. To define the value of pre-RIC/NMA HCT consolidation chemotherapy for AML in CR1, we addressed this question in a large dataset from the CIBMTR.

METHODS

Data Source

The CIBMTR includes a voluntary working group of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous HCT to a Statistical Center at the Medical College of Wisconsin in Milwaukee and the National Marrow Donor Program Coordinating Center in Minneapolis. Participating centers are required to report all transplants consecutively; patients are followed

longitudinally, and compliance is monitored by on-site audits. Computerized checks for discrepancies, physicians' review of submitted data, and on-site audits of participating centers ensure data quality. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected Health Information used in the performance of such research is collected and maintained in CIBMTR's capacity as a Public Health Authority under the HIPAA Privacy Rule.

Patient Selection

All adult patients reported to the CIBMTR who received a RIC or NMA conditioning HCT for AML in CR1 from either an HLA-identical sibling, unrelated donor (URD), or umbilical cord blood (UCB) donor from 2000 to 2010 were included in this analysis. Patients with French American British (FAB) subtype M3 were excluded. The very few patients with favorable risk cytogenetics ($n = 8$) were also excluded.

A total of 604 patients was identified from 165 centers. Patients were initially divided into 3 cohorts for analysis: (1) no postremission therapy before transplant, (2) standard-dose cytarabine consolidation therapy (defined as ≤ 1 g/m²/day on earlier CIBMTR data submission forms [pre-2008] or ≤ 2 g/m²/day on current forms), or (3) high-dose cytarabine consolidation therapy (defined as > 1 g/m²/day on earlier forms or > 2 g/m²/day on current forms). However, because no difference was seen between lower and higher dose consolidation cohorts, the final analysis compared no cytarabine consolidation versus any dose of cytarabine consolidation.

Patients included in the study cohort received a maximum of 2 cycles of induction therapy to obtain CR1 status. CIBMTR classifications of URD matching were used to define well-matched, partially matched, or mismatched categories [15]. Preparative regimens were classified as either RIC or NMA by established CIBMTR functional definitions. RIC included any regimen with either (1) 500 cGy or less of total body irradiation as a single fraction or 800 cGy or less if fractionated (2) < 9 mg/kg busulfan oral (or intravenous equivalent), (3) < 140 mg/m² melphalan, (4) < 10 mg/kg thiopeta, or (5) BEAM regimen (carmustine, etoposide, cytarabine, and melphalan) [16,17]. All other regimens were classified as NMA conditioning according to Champlin et al. [18] where prompt hematopoietic recovery could reasonably be expected without a transplant and would produce mixed chimerism after engraftment post-transplant. Based on these classifications, the most common RIC regimens included (1) fludarabine + busulfan, (2) fludarabine + melphalan, (3) fludarabine + cyclophosphamide, and (4) other. NMA regimens included fludarabine + low-dose total body irradiation (≤ 200 cGy) and fludarabine + antithymocyte globulin.

Study Endpoints

The primary endpoint was overall survival (OS) in those with or without pre-HCT consolidation chemotherapy. Secondary endpoints included hematopoietic recovery, occurrence of acute and chronic graft-versus-host disease (GVHD), TRM, incidence of relapse, and disease-free survival (DFS). OS was defined as time to death from any cause with surviving patients censored at time of last contact. Hematopoietic recovery was defined as time to absolute neutrophil count ≥ 500 neutrophils/ μ L sustained for 3 consecutive days. Criteria for acute and chronic GVHD were based on consensus criteria as previously defined [19,20]. TRM was defined as any death in the first 28 days post-transplant or any death after day 28 without recurrent leukemia. Relapse was defined as hematologic evidence of disease recurrence with those surviving without relapse censored at the date of last contact and using death in remission as the competing hazard. DFS was defined as survival without death or relapse with those who survived without recurrence or persistent disease censored at the date of last contact.

Statistical Analysis

Patient, disease, treatment history, and transplant-related factors were compared between groups using the chi-square test for categorical variables and the Wilcoxon two-sample test for continuous variables. The product-limit estimator proposed by Kaplan and Meier [21] was used to estimate the median and range of follow-up time.

Univariate probabilities of DFS and OS were calculated using the Kaplan-Meier estimator with the variance estimated by Greenwood's formula [21]. Probabilities of acute and chronic GVHD, TRM, and relapse were calculated using cumulative incidence curves to accommodate competing risks. Ninety-five percent confidence intervals (CIs) for all probabilities and *P* values of pairwise comparisons were derived from pointwise estimates and calculated using an arcsine square root transformation.

The final consolidation therapy groups used for analysis were no consolidation versus any dose cytarabine consolidation after initial analyses showing no cytarabine dose effect. The proportional hazards assumption for all variables was examined and its violations addressed by using a stratified Cox model when needed. A backward elimination method was used to build the regression model for the outcomes of TRM, relapse, DFS, and OS. Because exposure to cytarabine-based consolidation was the main interest of the study, the risk factor of cytarabine consolidation was included in all steps of model building. Patient-related variables, including age (<45, 45 to 60, >60), gender, and Karnofsky Performance Status (<90 versus ≥90%), were considered in the analysis. Disease-related variables included FAB or World Health Organization subtype (FAB M0/M1/M2 versus M4/M5/M6/M7 versus AML Not Otherwise Specified versus all remaining categories versus missing), antecedent hematologic disorder (yes or no), cytogenetics at diagnosis by Southwest Oncology Group criteria [2] (intermediate versus unfavorable versus unknown significance), and number of cycles of induction chemotherapy (1 versus 2). Transplant-related variables included year of transplant (2000 to 2005 versus 2006 to 2008 versus 2008 to 2010), donor source (matched sibling versus matched URD versus UCB versus other URD), recipient cytomegalovirus serostatus (negative versus positive versus missing), conditioning regimen (fludarabine + busulfan versus fludarabine + melphalan versus fludarabine + cyclophosphamide and "other" versus NMA), GVHD prophylaxis (tacrolimus based versus cyclosporine based), and antithymocyte globulin or alemtuzumab exposure (yes or no).

Risk factors with a significance level of *P* < .05 were included in the model. The potential interaction between main effect of pretransplant consolidation therapy exposure and all significant covariates were examined. Adjusted probability of DFS and OS were computed based on the final Cox regression model, stratified by age, and weighted by the pooled sample proportion value for all significant risk factors. SAS software (SAS Institute, Cary, NC) was used to perform all statistical analyses.

RESULTS

Patient disease, treatment, and transplant-related factors are shown in Table 1. All patients received induction chemotherapy with either 3 + 7 based (anthracycline + cytarabine) (85%) or other multidrug induction regimens including mitoxantrone and etoposide (4%), cytarabine regimens without anthracycline (9%), and others (2%) (clofarabine, gemtuzumab, topotecan, amsacrine, enocitabine, or anthracycline alone). Median age, performance status, presence of extramedullary disease, median WBC count at diagnosis, graft source, type of GVHD prophylaxis, and use of antithymocyte globulin or alemtuzumab were similar between the 2 groups.

Between the consolidation groups, those receiving no consolidation had a slightly higher percentage of AML Not Otherwise Specified (25% compared with 18%), had a slightly higher percentage of "other" multiagent induction chemotherapy (22% versus 11%), were more likely to have previously undergone 2 cycles of induction before CR1 documentation (33% versus 19%), and were more likely to have an antecedent hematologic disorder (myelodysplastic syndrome/myeloproliferative neoplasm) (34% versus 19%). Those receiving no consolidation also had a slightly higher percentage of fludarabine + melphalan conditioning (25% versus 13%) compared with the cytarabine consolidation group. Those receiving no cytarabine consolidation were slightly less likely to be classified as an FAB subtype of M4/M5/M6/M7 (20% versus 32%) and have intermediate risk cytogenetics (38% versus 48%). The median follow-up between the groups was similar (36 months for no consolidation versus 35 months for those receiving consolidation).

Outcomes

After a median follow-up of 36 months (range, 3 to 132), 239 patients were alive at last contact. Two hundred seventeen patients had relapsed and died, and 20 patients had relapsed but were alive at last contact.

Three-year OS was similar between the groups: 36% (95% CI, 29% to 43%) for those receiving no consolidation compared with 42% (95% CI, 37% to 47%) in the consolidation group (*P* = .15) (Figure 1). There was no significant difference in the incidence of relapse. The no consolidation group had a 3-year cumulative incidence of relapse of 37% (95% CI, 33% to 43%) versus the consolidation group at 38% (95% CI, 33% to 43%; *P* = .80) (Figure 2).

Neutrophil engraftment at Day +28 was similar between groups, with no consolidation at 86% (95% CI, 77% to 92%) and consolidation at 82% (95% CI, 75% to 87%). The cumulative incidence of grades III to IV acute GVHD was similar at 16% (95% CI, 12% to 22%) and 13% (95% CI, 10% to 16%), respectively (*P* = .26). The incidence of chronic GVHD at 3 years was identical between the 2 groups at 41% (*P* = .96).

TRM at Day +100 was slightly higher in the no consolidation group at 12% (95% CI, 8% to 17%) compared with 5% (95% CI, 4% to 8%) in the consolidation group (*P* = .01). This difference was maintained at 1 year with a TRM of 23% (95% CI, 17% to 29%) in the no consolidation group versus 16% (95% CI, 12% to 20%) in the consolidation group (*P* = .04).

Three-year DFS for the no consolidation group was 34% (95% CI, 27% to 41%) compared with 41% (95% CI, 35% to 46%) for the group receiving consolidation (*P* = .15) (Table 2). Additional supplemental univariate analyses investigating the impact of cytogenetic risk group, type of induction chemotherapy, conditioning regimen, and donor source on post-HCT outcomes revealed no unique factors of significance (data not shown). These analyses found that unfavorable cytogenetics, UCB donor source, and fludarabine plus melphalan conditioning were the only factors of significance influencing relapse or TRM, mirroring the findings of our primary analysis focusing on cytarabine consolidation exposure.

A forward stepwise method was used to build the regression models and compare risks for TRM, relapse, DFS, and OS in multivariate analyses, adjusting for the effects of other significant covariates (Table 3). Similar outcomes regardless of consolidation exposure were confirmed for OS, DFS, and relapse. The modest univariate difference in TRM between the 2 groups was not confirmed in multivariate analysis. Unfavorable cytogenetics was the only significant factor influencing relapse. TRM was worse with UCB donor source, fludarabine + melphalan conditioning, and age > 60 but was better in women. OS was worse with UCB donor source, unfavorable cytogenetics, age > 60, and male gender.

DISCUSSION

In persons with AML in CR1 receiving a RIC/NMA allogeneic HCT, we found no difference in outcomes between those who did or did not receive pre-HCT cytarabine consolidation. Our data highlight similar OS, DFS, and relapse post-RIC/NMA HCT with no increased TRM after cytarabine consolidation. The precise evaluation of potential benefit or harm of giving cytarabine consolidation requires a randomized trial; however, no such study is reported or likely to be completed. These results are similar to the findings previously reported by others in the MA setting [5,6].

Because the use of RIC regimens for HCT continues to expand, efforts to optimize both efficacy and safety of

Table 1
Characteristics of Adult Patients (≥18 Years) Receiving RIC/NMA HCT for AML in CR1 between 2000 and 2010

Characteristics	No Cytarabine Consolidation	Cytarabine Consolidation	P
No. of patients	202	402	
No. of centers	90	75	
Patient-related characteristics			
Age at transplant, yr, median (range)	60 (18–75)	59 (19–76)	.18
Age			.29
Less than 45 years	21 (10%)	41 (10%)	
45–60	76 (38%)	177 (44%)	
Greater than 60	105 (52%)	184 (46%)	
Gender			.16
Male	125 (52%)	225 (55%)	
Female	77 (38%)	177 (45%)	
Karnofsky Performance Status			.84
90%–100%	133 (66%)	268 (67%)	
Less than 90%	60 (30%)	120 (30%)	
Missing	9 (4%)	14 (3%)	
Disease-related characteristics			
FAB subtype			<.01
M0/M1/M2	64 (32%)	139 (35%)	
M4/M5/M6/M7	40 (20%)	127 (32%)	
AML NOS	51 (25%)	74 (18%)	
Miscellaneous	21 (10%)	31 (7.5%)	
Other/missing	26 (13%)	31 (7.5%)	
WBC count at diagnosis			.16
≥ to $5 \times 10^7/L$	110 (54%)	195 (49%)	
< $5 \times 10^7/L$	92 (46%)	207 (51%)	
Extramedullary disease at diagnosis			.67
Absent	193 (96%)	382 (95%)	
Present	8 (4%)	44 (5%)	
Cytogenetics (SWOG classification)			.03
Intermediate	77 (38%)	193 (48%)	
Unfavorable	63 (31%)	119 (30%)	
Unknown significance	62 (31%)	90 (22%)	
Pre-existing MDS/MPN			<.01
No	134 (66%)	327 (81%)	
Yes	68 (34%)	75 (19%)	
Time from diagnosis to CR1, mo, median (range)	1.6 (<1–89)	1.3 (<1–160)	<.0001
0–2	120 (59%)	306 (76%)	
2–6	60 (30%)	88 (22%)	
6+	22 (11%)	8 (2%)	
Treatment characteristics			
Induction regimen			<.01
3 + 7 or “similar”	157 (78%)	358 (89%)	
Other multiagent induction	45 (22%)	44 (11%)	
Cycles of induction chemotherapy			<.01
1	136 (67%)	326 (81%)	
2	66 (33%)	76 (19%)	
Cycles of cytarabine consolidation			
1	N/A	168 (42%)	
2 or more	N/A	134 (33%)	
Unknown number	N/A	100 (25%)	
Year of transplant			<.01
2000–2005	53 (26%)	106 (26%)	
2006–2008	84 (42%)	148 (37%)	
2008–2010	65 (32%)	148 (37%)	
Graft source			.51
Matched sibling donor	106 (52%)	185 (46%)	
Matched URD	52 (26%)	117 (29%)	
Partially matched URD	16 (8%)	38 (9%)	
UCB	28 (14%)	62 (15%)	
Recipient CMV serostatus			.29
Negative	61 (30%)	128 (32%)	
Positive	141 (70%)	269 (67%)	
Missing	0 (0%)	5 (1%)	
Conditioning regimens			
RIC			.045
Flu/Bu	89 (44%)	173 (43%)	

(Continued)

Table 1
(Continued)

Characteristics	No Cytarabine Consolidation	Cytarabine Consolidation	P
Flu/Mel	51 (25%)	54 (13%)	
Flu/Cy + other	36 (18%)	97 (24%)	
NMA			
Flu/TBI (200–500 cGy)	23 (11%)	71 (18%)	
Flu/ATG	3 (2%)	7 (2%)	
GVHD prophylaxis			.32
Tacrolimus based	115 (57%)	212 (53%)	
Cyclosporine based	87 (43%)	190 (47%)	
ATG/alemtuzumab use			.06
No	133 (66%)	235 (58%)	
Yes	69 (34%)	167 (42%)	
Time from CR1 to transplant, mo, median (interquartile range, 25%–75%)	2 (1–4)	4 (3–5)	<.0001
Follow-up of survivors, mo, median (range)	36 (3.9–115)	35 (3.2–132)	.25

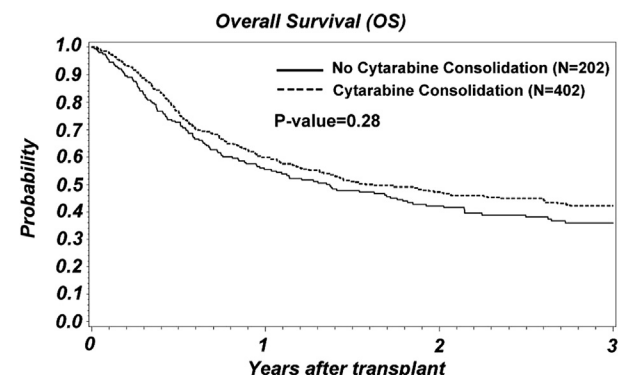
NOS indicates Not Otherwise Specified; SWOG, Southwest Oncology Group; MDS, myelodysplastic syndrome; MPN, myeloproliferative neoplasm; CMV, cytomegalovirus; Flu, fludarabine; Bu, busulfan; Mel, melphalan; Cy, cyclophosphamide; TBI, total body irradiation; ATG, antithymocyte globulin.

Miscellaneous AML subtypes included AML with abnormal eosinophils + AML with 11q23 + AML with multilineage dysplasia; induction chemotherapy: 3 + 7 = anthracycline (idarubicin or daunorubicin) + cytarabine; other multiagent induction (n = 89) included mitoxantrone + etoposide (4%), cytarabine without anthracycline (9%), and others (2%) (clofarabine, gemtuzumab, topotecan, amsacrine, enocitabine, anthracycline alone).

therapy continue. Several retrospective studies comparing MA conditioning with RIC have suggested an increased risk of relapse with RIC accompanied in some series by improved TRM [7–9], suggesting that RIC conditioning is potentially less effective in control of residual leukemia during CR. However, more recent studies [11–13] have revealed similar relapse, TRM, and OS regardless of conditioning intensity for AML patients transplanted in CR. The finding that post-HCT outcomes are not improved by cytarabine consolidation chemotherapy before RIC/NMA HCT supports the contention that RIC can effectively control disease recurrence in CR1 AML and may challenge many clinicians' preconceived theories.

Only limited data have been available to help guide consolidation chemotherapy decision-making before a RIC/NMA HCT. McCormack et al. [14] described the University of Minnesota experience with similar survival and relapse rates

Similar Survival Based on Exposure to Cytarabine Consolidation

**Figure 1.** Comparison of survival post-transplant between AML CR1 subjects who did or did not receive pretransplant cytarabine consolidation.

Similar Incidence of Post-HCT Relapse Regardless of Pre-HCT Cytarabine Consolidation

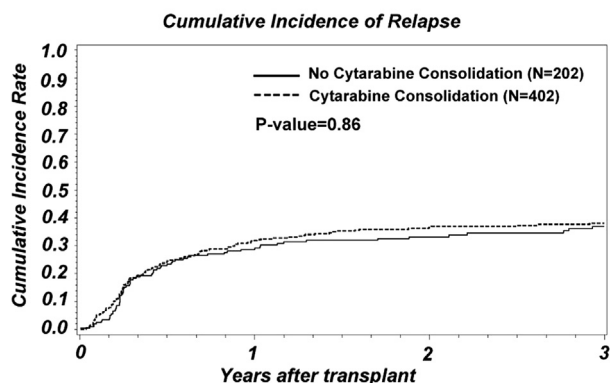


Figure 2. Comparison of post-transplant relapse incidence between AML CR1 subjects who did or did not receive pretransplant cytarabine consolidation.

regardless of cytarabine consolidation using a uniform RIC regimen for AML. The current larger study, with diverse conditioning regimens, reveals similar findings and has substantially more power to identify any potentially differing outcomes regardless of cytarabine consolidation exposure—and none was found.

Pretransplant cytarabine consolidation did not increase the risk of TRM. Physicians may, however, choose patients with a better performance status to receive consolidation chemotherapy before HCT and proceed directly to HCT for those patients who tolerated induction chemotherapy poorly or alternatively choose consolidation in those with higher relapse risks. We do not have data to directly examine the treating physician rationale for giving consolidation chemotherapy before RIC HCT. Our multivariate analysis did not demonstrate any difference in TRM based on consolidation exposure but did show higher TRM after UCB HCT in men, in those receiving fludarabine plus melphalan–based conditioning, and in those older than 60.

Our analysis was designed to investigate cytarabine consolidation but also any potential cytarabine dose effect. In the past, the advantage of high dose cytarabine consolidation without HCT was noted primarily for persons with good risk

cytogenetics [1] or younger patients (<60 years) with normal cytogenetics [22]. Thus, it is not surprising that we found similar outcomes regardless of cytarabine dose in this dataset that excluded patients with good risk cytogenetics and included a large subset of patients over the age of 60 [1,22,23]. These data support the theory that in AML patients in CR1, the graft-versus-leukemia effect provided by the allograft can eliminate residual disease in long-term survivors, even after RIC/NMA HCT. We analyzed only patients in morphologic CR as reported by the participating centers. Emerging literature suggest that minimal residual disease defined by either cytogenetic, molecular, or multiparameter flow cytometry, may influence post-HCT outcomes and may identify patients with higher risk of relapse [24,25]. Future analysis should consider depth of remission defined by cytogenetic, molecular, and flow cytometric data to investigate the value of added pre-HCT cytarabine or other consolidation to reduce tumor burden before RIC allogeneic HCT, but these data suggest lesser importance of this minimal disease burden during CR1.

We acknowledge the inherent limitations of an analysis using an observational database. We cannot account for those who relapsed before HCT and were excluded, yet the median time to HCT we studied was only 2 and 4 months for the 2 cohorts, capturing most of the higher risk period. In addition, some differences between the 2 groups merit discussion. Those requiring 2 rounds of induction before CR1 more often had no consolidation. However, it is uncertain if 2 rounds of induction chemotherapy were given after the absence of a remission after the first induction cycle. More patients in the no consolidation group had preceding myelodysplastic syndrome/myeloproliferative neoplasm, another factor that might favor the consolidation arm. Finally, in this dataset we did not have the important data regarding FLT-3 ITD and NPM1 mutational status. Given this limitation, application of these data to those with known molecular signatures implying increased relapse risk, such as FLT-3 ITD, would not be recommended. In the absence of those molecular signatures, however, the results clearly show no difference in outcome based on pre-HCT consolidation exposure and support a recommendation to proceed promptly to transplant as soon as CR1 is attained. If HCT is delayed by the time required to identify a suitable donor, our data suggest that

Table 2
Outcomes after RIC/NMA HCT Based on Cytarabine Consolidation Exposure: Univariate Analysis

	No Cytarabine Consolidation		Cytarabine Consolidation		P
	No. Assessable	Incidence (95% CI)	No. Assessable	Incidence (95% CI)	
OS					
At 2 yr	202	42 (35–49)	402	47 (42–52)	.25
At 3 yr	202	36 (29–43)	402	42 (37–47)	.16
Relapse					
At 2 yr	197	33 (27–40)	393	37 (32–41)	.42
At 3 yr	197	37 (30–44)	393	38 (33–43)	.80
Acute GVHD grades III–IV	202		402		
At Day +100		16 (12–22)		13 (10–16)	.26
Chronic GVHD	195		395		
At 3 yr		41 (34–49)		41 (36–47)	.96
TRM					
At 100 d	197	12 (8–17)	393	5 (4–8)	.01
At 1 yr	197	23 (17–29)	393	16 (12–20)	.04
DFS					
At 2 yr	197	39 (32–46)	393	44 (39–49)	.20
At 3 yr	197	34 (27–41)	393	41 (35–46)	.15

Table 3
Outcome after RIC/NMA HCT: Multivariate Analysis

Outcome	Variable	Relative Risk	95% CI	P
OS	Consolidation			
	No	1		
	Yes	.886	.71-1.10	.28
	Donor source			
	Matched sibling	1		
	Matched URD	.88	.68-1.14	.34
	Partially matched URD	1.03	.71-1.51	.86
	UCB	1.60	1.18-2.16	.002
	Cytogenetics			
	Intermediate	1		
	Unfavorable	1.74	1.36-2.22	<.0001
	Other/missing	1.20	.92-1.56	.18
	Age			
	<45	1		
	45-60	1.22	.83-1.79	.31
	>60	1.51	1.03-2.2	.03
	Gender			
	Male	1		
	Female	.78	.63-.97	.02
TRM	Consolidation			
	No	1		
	Yes	.74	.53-1.04	.08
	Donor source			
	Matched sibling	1		
	Matched URD	.998	.65-1.52	.99
	Partially matched URD	1.371	.79-2.39	.26
	UCB	3.83	2.25-6.54	<.0001
	Conditioning			
	Flu/Bu	1		
	Flu/Mel	1.6	1.05-2.43	.03
	Flu/other	.65	.38-1.14	.13
	TBI based	.94	.56-1.6	.80
	Age			
	<45	1		
	45-60	1.2	.63-2.28	.58
	>60	1.96	1.04-3.67	.04
	Gender			
	Male	1		
	Female	.65	.46-.91	.013
Relapse	Consolidation			
	No	1		
	Yes	1.03	.77-1.36	.86
	Cytogenetics			
	Intermediate	1		
	Unfavorable	1.87	1.38-2.5	<.0001
	Other/missing	1.17	.83-1.66	.37
	WBC count			
	<5.0	1		
	≥5.0	.77	.59-.99	.05
DFS	Consolidation			
	No	1		
	Yes	.87	.7-1.07	.19
	Cytogenetics			
	Intermediate	1		
	Unfavorable	1.65	1.29-2.1	<.0001
	Other/missing	1.19	.92-1.55	.19
	Gender			
	Male	1		
	Female	.75	.60-.92	.0071
	Donor source			
	Matched sibling donor	1		
	Matched URD	.84	.64-1.09	.20
	Partially matched URD	.94	.64-1.36	.72
	UCB	1.37	1.01-1.85	.04

Relapse and DFS models were stratified on ATG/alemtuzumab use.

consolidation does not increase HCT TRM and its use is acceptable in that setting.

ACKNOWLEDGMENTS

The authors acknowledge contributions to protocol development from the following individuals: Alison W.

Loren, Ann E. Woolfrey, Ayman Saad, Camille Abboud, Dipnarine Maharaj, Edward A. Copelan, Franklin O. Smith, Jeffrey Szer, Jacob M. Rowe, James M. Foran, James L. Gajewski, Joseph H. Antin, Joseph Pidala, H. Kent Holland, Martin S. Tallman, Maxim Norkin, Michael R. Bishop, Mitchell S. Cairo, Muthalagu Ramanathan, Rodrigo Martino, Peter H. Wiernik, Robert K. Stuart, Stella Santarone, and William R. Drobyski.

Financial disclosure: The CIBMTR is supported by Public Health Service Grant/Cooperative Agreement U24 CA076518 from the National Cancer Institute (NCI), the National Heart, Lung and Blood Institute (NHLBI), and the National Institute of Allergy and Infectious Diseases; Grant/Cooperative Agreement U10 HL069294 from the NHLBI and NCI; contract HHS250201200016C from Health Resources and Services Administration/US Department of Health and Human Services; 2 grants (N00014-12-1-0142 and N00014-13-1-0039) from the Office of Naval Research; and grants from Allos Therapeutics, Inc.; Amgen, Inc.; Anonymous donation to the Medical College of Wisconsin; Ariad; Be the Match Foundation; Blue Cross and Blue Shield Association; Celgene Corporation; Fresenius-Biotech North America, Inc.; Gamida Cell Teva Joint Venture Ltd.; Genentech, Inc.; Gentium SpA; Genzyme Corporation; GlaxoSmithKline; Histogenetics, Inc.; Kiadis Pharma; The Leukemia & Lymphoma Society; The Medical College of Wisconsin; Merck & Co, Inc.; Millennium: The Takeda Oncology Co.; Milliman USA, Inc.; Miltenyi Biotec, Inc.; National Marrow Donor Program; Onyx Pharmaceuticals; Optum Healthcare Solutions, Inc.; Osiris Therapeutics, Inc.; Otsuka America Pharmaceutical, Inc.; Remedy Informatics; Sanofi US; Seattle Genetics; Sigma-Tau Pharmaceuticals; Soligenix, Inc.; StemCyte, A Global Cord Blood Therapeutics Co.; Stemsoft Software, Inc.; Swedish Orphan Biovitrum; Tarix Pharmaceuticals; TerumoBCT; Teva Neuroscience, Inc.; THERAKOS, Inc.; and Wellpoint, Inc. The views expressed in this article do not reflect the official policy or position of the National Institutes of Health, the Department of the Navy, the Department of Defense, or any other agency of the US Government.

Conflict of interest statement: J. K. has compensated consultant/advisory relationships with Spectrum Pharmaceuticals and Eleven Biotherapeutics; honoraria from Optum Health; and research funding from Millennium Pharmaceuticals, Otsuka Pharmaceuticals, and Prometheus Cabs.

REFERENCES

- Mayer RJ, Davis RB, Schiffer CA, et al. Intensive postremission chemotherapy in adults with acute myeloid leukemia. Cancer and leukemia group B. *N Engl J Med*. 1994;331:896-903.
- Slovak ML, Kopecky KJ, Cassileth PA, et al. Karyotypic analysis predicts outcome of preremission and postremission therapy in adult acute myeloid leukemia: A Southwest Oncology Group/Eastern Cooperative Oncology Group study. *Blood*. 2000;96:4075-4083.
- Grimwade D, Hills RK, Moorman AV, et al. Refinement of cytogenetic classification in acute myeloid leukemia: Determination of prognostic significance of rare recurring chromosomal abnormalities among 5876 younger adult patients treated in the United Kingdom medical research council trials. *Blood*. 2010;116:354-365.
- Koreth J, Schlenk R, Kopecky KJ, et al. Allogeneic stem cell transplantation for acute myeloid leukemia in first complete remission: Systematic review and meta-analysis of prospective clinical trials. *JAMA*. 2009;301:2349-2361.
- Tallman MS, Rowlings PA, Milone G, et al. Effect of postremission chemotherapy before human leukocyte antigen-identical sibling transplantation for acute myelogenous leukemia in first complete remission. *Blood*. 2000;96:1254-1258.
- Cahn J, Labopin M, Sierra J, et al. No impact of high-dose cytarabine on the outcome of patients transplanted for acute myeloblastic leukaemia in first remission. Acute Leukaemia Working Party of the European Group for Blood and Marrow Transplantation (EBMT). *Br J Haematol*. 2000;110:308-314.

7. Alyea EP, Kim HT, Ho V, et al. Comparative outcome of non-myeloablative and myeloablative allogeneic hematopoietic cell transplantation for patients older than 50 years of age. *Blood*. 2005;105:1810-1814.
8. Alyea EP, Kim HT, Ho V, et al. Impact of conditioning regimen intensity on outcome of allogeneic hematopoietic cell transplantation for advanced acute myelogenous leukemia and myelodysplastic syndrome. *Biol Blood Marrow Transplant*. 2006;12:1047-1055.
9. Martino R, Iacobelli S, Brand R, et al. Retrospective comparison of reduced-intensity conditioning and conventional high-dose conditioning for allogeneic hematopoietic stem cell transplantation using HLA-identical sibling donors in myelodysplastic syndromes. *Blood*. 2006;108:836-846.
10. Martino R, Valcarcel D, Brunet S, et al. Comparable non-relapse mortality and survival after HLA-identical sibling blood stem cell transplantation with reduced or conventional-intensity preparative regimens for high-risk myelodysplasia or acute myeloid leukemia in first remission. *Bone Marrow Transplant*. 2008;41:33-38.
11. Luger SM, Ringden O, Zhang MJ, et al. Similar outcomes using myeloablative vs reduced-intensity allogeneic transplant preparative regimens for AML or MDS. *Bone Marrow Transplant*. 2012;47:203-211.
12. Bornhauser M, Kienast J, Trenschel R, et al. Reduced-intensity conditioning versus standard conditioning before allogeneic haematopoietic cell transplantation in patients with acute myeloid leukaemia in first complete remission: A prospective, open-label randomised phase 3 trial. *Lancet Oncol*. 2012;13:1035-1044.
13. Ringden O, Erkers T, Aschan J, et al. A prospective randomized toxicity study to compare reduced-intensity and myeloablative conditioning in patients with myeloid leukemia undergoing allogeneic haematopoietic stem cell transplantation. *J Intern Med*. 2013;274:153-162.
14. McCormack SE, Cao Q, Oran B, et al. Pre-transplant consolidation chemotherapy may not improve outcomes after reduced intensity conditioning hematopoietic stem cell transplantation for acute myeloid leukemia in first complete remission. *Leuk Res*. 2011;35:757-761.
15. Weisdorf D, Spellman S, Haagenson M, et al. Classification of HLA-matching for retrospective analysis of unrelated donor transplantation: Revised definitions to predict survival. *Biol Blood Marrow Transplant*. 2008;14:748-758.
16. Giral S, Ballen K, Rizzo D, et al. Reduced-intensity conditioning regimen workshop: Defining the dose spectrum. Report of a workshop convened by the Center for International Blood and Marrow Transplant Research. *Biol Blood Marrow Transplant*. 2009;15:367-369.
17. Bacigalupo A, Ballen K, Rizzo D, et al. Defining the intensity of conditioning regimens: Working definitions. *Biol Blood Marrow Transplant*. 2009;15:1628-1633.
18. Champlin R, Khouri I, Shimoni A, et al. Harnessing graft-versus-malignancy: Non-myeloablative preparative regimens for allogeneic haematopoietic transplantation, an evolving strategy for adoptive immunotherapy. *Br J Haematol*. 2000;111:18-29.
19. Przepiorka D, Weisdorf D, Martin P, et al. 1994 consensus conference on acute GVHD grading. *Bone Marrow Transplant*. 1995;15:825-828.
20. Arai S, Jagasia M, Storer B, et al. Global and organ-specific chronic graft-versus-host disease severity according to the 2005 NIH consensus criteria. *Blood*. 2011;118:4242-4249.
21. Kaplan EL, Meier P. Nonparametric estimation from incomplete observations. *J Am Stat Assoc*. 1958;53:457-481.
22. Farag S, Ruppert A, Mrozek K, et al. Outcome of induction and post-remission therapy in younger adults with acute myeloid leukemia with normal karyotype: A cancer and leukemia group B study. *J Clin Oncol*. 2005;23:482-493.
23. Lowenberg B. Sense and nonsense of high-dose cytarabine for acute myeloid leukemia. *Blood*. 2013;121:26-28.
24. Buckley SA, Appelbaum FR, Walter RB. Prognostic and therapeutic implications of minimal residual disease at the time of transplantation in acute leukemia. *Bone Marrow Transplant*. 2012;48:630-641.
25. Walter RB, Gooley TA, Wood BL, et al. Impact of pretransplantation minimal residual disease, as detected by multiparametric flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute myeloid leukemia. *J Clin Oncol*. 2011;29:1190-1197.