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Authors

Bejanyan, Nelli
Zhang, Mei-Jie
Wang, Hai-Lin
et al.

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Pre-transplant Consolidation is Not Beneficial for Adults with ALL Undergoing Myeloablative Allogeneic Transplantation

Nelli Bejanyan[1], **Mei-Jie Zhang**[2,3], **Hai-Lin Wang**[3], **Aleksandr Lazaryan**[1], **Marcos de Lima**[4], **David I. Marks**[5], **Brenda M. Sandmaier**[6], **Veronika Bachanova**[1], **Jacob Rowe**[7], **Martin Tallman**[8], **Partow Kebriaei**[9], **Mohamed Kharfan-Dabaja**[10], **Robert Peter Gale**[11], **Hillard M. Lazarus**[12], **Celalettin Ustun**[1], **Edward Copelan**[13], **Betty Ky Hamilton**[14], **Gary Schiller**[15], **William Hogan**[16], **Shahrukh Hashmi**[17,18], **Matthew Seftel**[19], **Christopher G. Kanakry**[20], **Richard F. Olsson**[21,22], **Rodrigo Martino**[23], **Wael Saber**[3], **H. Jean Khoury**[24], and **Daniel J. Weisdorf**[1]

[1]Division of Hematology, Oncology and Transplantation, University of Minnesota Medical Center, Minneapolis, MN

[2]Division of Biostatistics, Insitute for Health and Society, Medical College of Wisconsin, Milwaukee, WI

[3]CIBMTR (Center for International Blood and Marrrow Trasnsplantation), Department of Medicine, Medical College of Wisconsin, Milwaukee, WI

[4]Department of Medicine, Seidman Cancer Center, University Hospitals Case Medical Center, Cleveland, OH

[5]Adult Bone Marrow Transplant, University Hospitals Bristol NHS Trust, Bristol, United Kingdom

[6]Division of Medical Oncology, University of Washington and Clinical Research Division, Fred Hutchinson Cancer Research Center

[7]Department of Hematology, Shaare Zedek Medical Center, Jerusalem, Israel

[8]Leukemia Service, Department of Medicine, Memorial Sloan Kettering Cancer Center, New York, NY

[9]Department of Stem Cell Transplantation, Division of Cancer Medicine, The University of Texas MD Anderson Cancer Center

Authorship

Contribution: N.B., A.L. and D.J.W. conceived the study; M.J.Z. and H.L.W. analyzed and interpreted data; N.B. wrote the manuscript; N.B., H.J.K, M.J.Z., H.L.H., A.L., M.L., D.I.M., B.M.S., V.B., J.R., M.T., P.K., M.K.D., R.P.G., H.M.L., C.U., E.C., B.K.H., G.S., W.H., S.H., M.S., C.K., R.F.O., R.M., W.S. and D.J.W. interpreted and edited the manuscript; and all authors approved the final manuscript.

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[10]Department of Blood and Marrow Transplantation, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL

[11]Hematology Research Centre, Division of Experimental Medicine, Department of Medicine, Imperial College London, London, United Kingdom

[12]Seidman Cancer Center, University Hospitals Cleveland Medical Center, Cleveland, OH

[13]Department of Hematologic Oncology and Blood Disorders, Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC

[14]Blood & Marrow Transplant Program, Cleveland Clinic Taussig Cancer Institute, Cleveland, Ohio

[15]Hematological Malignancy/Stem Cell Transplant Program, David Geffen School of Medicine at UCLA

[16]Departments of Hematology and Transplant Center, Mayo Clinic Rochester, Rochester, MN

[17]Department of Internal Medicine, Mayo Clinic, MN

[18]Oncology Center, King Faisal Specialist Hospital and Research Center, Riyadh, Saudi Arabia

[19]Department of Medical Oncology and Hematology, CancerCare Manitoba, Winnipeg, Canada

[20]Experimental Transplantation and Immunology Branch, Center for Cancer Research, National Cancer Institute, National Institutes of Health, Bethesda, MD

[21]Division of Therapeutic Immunology, Department of Laboratory Medicine, Karolinska Institutet, Stockholm, Sweden

[22]Centre for Clinical Research Sormland, Uppsala University, Uppsala, Sweden

[23]Divison of Clinical Hematology, Hospital de la Santa Creu i Sant Pau, Barcelona, Spain

[24]Emory University Hospital, Atlanta, GA

Abstract

Allogeneic hematopoietic cell transplantation (alloHCT) is curative for patients with acute lymphoblastic leukemia (ALL) who achieve complete remission (CR1) with chemotherapy. However, the benefit of consolidation chemotherapy remains uncertain in patients undergoing alloHCT. We compared clinical outcomes of 524 adult patients with ALL in CR1 who received ≥ 2 (n=109), 1 (n=93), or 0 cycles (n=322) of consolidation prior to myeloablative alloHCT from 2008–2012. As expected, time to alloHCT was longer with increasing cycles of consolidation. Patients receiving ≥2, 1, or 0 cycles of consolidation had an adjusted 3-year cumulative incidence of relapse of 20%, 27%, and 22%; 1-year transplant-related mortality (TRM) of 16%, 18%, and 23%; adjusted 3-year leukemia-free survival (LFS) of 54%, 48%, and 47%; and 3-year overall survival (OS) of 63%, 59%, and 54% (all *p*-values >0.4). Multivariable analysis confirmed that consolidation was not prognostic for LFS (RR=1.20, 95% CI 0.86–1.67; p=0.28 for no consolidation; RR=1.18, 95% CI 0.79–1.76; p=0.41 for 1 cycle vs. ≥2 cycles=reference). Similarly, consolidation was not associated with OS, relapse, TRM, or GVHD. We conclude that consolidation chemotherapy does not appear to provide added benefit in adult ALL patients with available donors who undergo myeloablative alloHCT in CR1.

Keywords

ALL; consolidation chemotherapy; myeloablative conditioning; allogeneic transplant

INTRODUCTION

Allogeneic hematopoietic cell transplantation (alloHCT) is a potentially curative treatment for adult acute lymphoblastic leukemia (ALL) patients achieving initial complete remission (CR1) with cytoreductive chemotherapy.[1–3] Although most adult ALL treatment protocols include post-remission consolidation chemotherapy, it remains uncertain whether consolidation is beneficial in patients with an immediately available donor who is being considered for a prompt alloHCT. The MRC UKALL XII/ECOG 2993 trial mandated 2 cycles of induction chemotherapy (phase I and phase II) followed by intensification with high-dose methotrexate for adult ALL patients assigned to alloHCT arm, even when CR1 was achieved after initial phase 1 induction. [1, 4] Similarly, the GRAALL-2003 and LALA-94 prospective study protocols allowed alloHCT for high-risk CR1 ALL only after completion of several cycles of post-induction consolidation chemotherapy.[5, 6] In contrast, other ALL induction protocols allowed patients with available donors to proceed with alloHCT whenever CR1 was achieved.[7–9] Since time from CR to post-remission therapy has been found to be an independent predictor for relapse and overall survival (OS) in adults with ALL,[10] post-remission consolidation chemotherapy is routinely used in clinical practice while the donor search is in progress. However, among ALL patients in CR1 with an available allogeneic donor, the impact of further consolidation chemotherapy on clinical outcomes after transplantation remains uncertain. We hypothesized that consolidation chemotherapy is not associated with a survival benefit among alloHCT recipients with adult ALL in CR1. Therefore, we sought to determine the role of pre-transplant consolidation chemotherapy in adult ALL in CR1 prior to an early (as soon as CR is achieved) vs. delayed (post-consolidation) alloHCT therapeutic strategy for patients with an available donor.

METHODS

Data Source

The Center of International Blood and Marrow Transplant Research (CIBMTR) collects detailed data on consecutive alloHCT from a volunteer network of more than 450 transplant centers worldwide. CIBMTR data is reported to a centralized statistical center of the research headquarters located at the Medical College of Wisconsin and the National Marrow Donor Program. Patients reported to the CIBMR are longitudinally observed on a yearly basis. Data quality is ensured via computerized checks for errors and on-site audits. All observational studies conducted by the CIBMR are in compliance with all applicable federal regulations in order to ensure the protection of all human research subjects. The Institutional Board and the Privacy Officer of the Medical College of Wisconsin granted a waiver of informed consent for the present study that is in compliance with Health Insurance Portability and Accountability Act regulations.

Patient Selection

We included patients aged 16 years and older with ALL in CR1 who received their first myeloablative alloHCT from 2008 to 2012. Patients were excluded if they had French American British (FAB) type L3 ALL (Burkitt's leukemia), received transplant from an identical twin or haploidentical related donor, or were missing their 100-day comprehensive research data collection form or informed consent form, or those missing pre-HCT treatment details. Conditioning intensity was defined using CIBMTR's consensus criteria.[11] In-vivo T-cell depletion was defined as use of antithymocyte globulin (ATG) or alemtuzumab in conditioning. HLA-matching for unrelated donor (URD) transplantation was classified using recommended criteria by CIBMTR.[12] Poor risk cytogenetics was defined as a complex karyotype with ≥3 chromosomal abnormalities, hypodiploid karyotype, or chromosomal translocations t(9;22), t(4;11), t(8;14), and t(14;18). Other cytogenetic risk was defined as having normal karyotype or chromosomal abnormalities other than poor cytogenetics. We defined remission induction chemotherapy cycles as those intensive chemotherapy cycles administered before achieving CR1. CR was defined as no morphological evidence of leukemia and <5% of bone marrow blasts after treatment.[13] We defined consolidation chemotherapy cycles as those intensive chemotherapy cycles administered after CR1, but prior to alloHCT. Intensive chemotherapy consisted of multi-agent cytoreductive chemotherapy regimens administrated such as HyperCVAD,[7, 8] CALGB,[9, 14–16] and MRC UKALL XII/ECOG 2993[1, 4] or similar ALL "adult" type treatment protocols. Tyrosine-kinase inhibitor (TKI) administration prior to or after transplantation was considered as TKI treatment or maintenance therapy. Central nervous system (CNS) leukemia prophylaxis was defined as receiving intrathecal chemotherapy, systemic high-dose intravenous (IV) methotrexate, cranial irradiation, spinal irradiation, or a combination thereof for prevention of CNS involvement with leukemia.

Study Endpoints

The primary endpoint of the study was LFS of ALL patients in CR1 receiving ≥2, 1, or 0 cycles of consolidation chemotherapy prior to alloHCT. LFS was defined as the time from transplantation to death or leukemia relapse. Secondary endpoints included treatment-related mortality (TRM), incidence of relapse (systemic or CNS), acute and chronic graft-versus-host disease (GVHD), and overall survival (OS). TRM was defined as death from any cause without any evidence of leukemia relapse considering relapse as a competing event. Acute and chronic GVHD grading was performed according to consensus criteria.[17, 18] Overall survival was defined as the time from transplant to death from any cause; patients who were alive and remained in CR were censored at the last follow-up.

Statistical Analysis

Chi-square test for categorical variables and Kruskal Wallis test for continuous variables were used to compare patient-, disease-, treatment-, and transplant-related characteristics between patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy prior to alloHCT. Univariate probabilities of LFS and OS were estimated by the Kaplan-Meier method. Cumulative incidence function was used to calculate probabilities of TRM, and relapse was considered a competing risk and the converse for relapse with TRM as a

competing risk. Potential risks factors for clinical outcomes were tested using Cox proportional hazards regression model. The assumption of proportional hazards for each factor was tested using time-dependent covariates, and a backward stepwise model was used to select all significant risk factors. Factors that were significant at a 5% level were retained in the final model. The main effect of consolidation cycle numbers, donor type and recipient age were included in each step of model building regardless of their significance, and the potential interactions between main effect and all significant covariates were tested. The variables that were considered in the multivariable models included number of consolidation cycles, recipient age, Karnofsky performance status (KPS), comorbidity index (HCT-CI), cytogenetic risk, WBC count at diagnosis, time from diagnosis to CR1, detectable disease status at transplant, recipient CMV serostatus, donor type, graft source, and in-vivo T-cell depletion. Adjusted probabilities of LFS and survival, and adjusted cumulative incidence functions of TRM and relapse were calculated using the multivariate models, stratified on cycles of consolidation (≥2 vs. 1 vs. 0) and weighted by the pooled sample proportion value for each prognostic factor.[19, 20] All study analyses were performed using SAS software (SAS institute, Vary, NC).

RESULTS

Patient Characteristics

We identified 524 adult patients with ALL in CR1 from 116 transplant centers undergoing alloHCT with myeloablative conditioning from 2008 to 2012: 109 patients received ≥2 cycles of consolidation chemotherapy, 93 patients received 1 cycle, and 322 patients received 0 cycles. Overall median follow-up of survivors was 59 months (6–79 months). Patient, disease, treatment and transplant characteristics are summarized in Table 1. The median age was 35, 36, and 40 years for patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy (p=0.01), respectively. In addition, there were no reported comorbidities at HCT in 56%, 69%, and 59% of patients receiving ≥2, 1, or 0 cycles of consolidation chemotherapy (p=0.04), respectively. Philadelphia positive chromosomal abnormality was present in 44% of all study patients, and only 21% of all patients had normal cytogenetics. Only a minority of patients had hyperleukocytosis (defined as white blood cell count of >100 x10^9/L; 8%) at diagnosis or CNS involvement by leukemia (9%) at any time point prior to HCT. An HLA-identical sibling donor was used in 205 (39%) patients, URD in 198 (38%; 150 well matched, 42 partially matched, and 6 mismatched), and UCB in 121 (23%; 33 single and 88 double UCB). Peripheral blood (63%) was the most commonly used graft source followed by UCB (23%) or bone marrow (14%). The majority of all patients (>80%) achieved CR1 with only one cycle of induction chemotherapy; however, the median time from diagnosis to CR1 was significantly longer among patients receiving no consolidation chemotherapy (2 months) than among patients receiving 1 cycle (1 month) or ≥2 cycles (1 month) of consolidation chemotherapy (p<0.001). In contrast and as expected, the median time from CR1 to HCT was longer for patients receiving ≥2 cycles (5 months) than for patients receiving 1 cycle (3 months) or no cycles (2 months) of consolidation chemotherapy (p<0.001). About half of patients (54%) receiving ≥2 cycles of consolidation received only two cycles of consolidation chemotherapy. Detectable minimal residual disease (MRD) status prior to HCT either by cytogenetics or by molecular

assessment was present only in a minority of patients in the entire cohort, and it was similar among the 3 groups (14%, 11% and 18% (p=0.12), respectively). For those receiving ≥2, 1, or 0 cycles of consolidation, pre-transplant CNS prophylaxis was used in 84%, 81%, or 70% (p=0.005) of patients; and pre- or post-HCT TKI maintenance chemotherapy among Philadelphia chromosome–positive (Ph+) patients (n=231) was used in 65%, 55%, or 46% (p=0.10), respectively. Other patient, disease, treatment and transplant characteristics were similar among the three study groups.

Relapse and Treatment-Related Mortality

The cumulative incidence of relapse at 3-years for ≥2, 1, or 0 cycles of consolidation chemotherapy was 20%, 26%, and 21%, respectively (p=0.71, Table 2 and Figure 1). In addition, when relapse was evaluated among the Ph+ subgroup of patients, we identified no influence of consolidation on risks of relapse after alloHCT. In multiple regression analysis consolidation chemotherapy did not influence risk of relapse (Table 3). In addition, MRD prior to HCT did not influence the relapse risk. Adjusted probabilities of 1-year TRM were 17%, 18%, and 23%, respectively (p=0.56). In univariable analysis, the donor type and graft source influenced TRM; however, none of the other factors tested were significantly associated with relapse incidence after alloHCT. Consolidation did not influence the risks of TRM, but the choice of partially/mismatched URD (mmURD, RR=3.11, 95%CI 1.87–5.18; p<.0001) or UCB donor (RR=2.46, 95%CI 1.64–3.71; p<.0001) significantly increased the risk of TRM after alloHCT.

Leukemia-Free Survival and Overall Survival

Univariate LFS probabilities at 3-years for ≥2, 1, and 0 cycles of consultation therapy were similar at 54%, 48%, and 48%, respectively (p-value =0.48). Similarly, univariate OS probabilities at 3-years were 63%, 58%, and 54%, respectively (p-value =0.21). Donor type was the only factor associated with LFS and OS. In contrast, LFS or OS were not affected by patient age, KPS, HCT-CI, cytogenetics, WBC count at diagnosis, detectable disease status prior to HCT, time from diagnosis to CR1, recipient CMV serostatus, *in vivo* T-cell depletion, or type of GVHD prophylaxis. In multiple regression analysis, consolidation chemotherapy did not influence treatment failure (inverse of LFS) or overall mortality. mmURD and UCB donor types increased the risk of treatment failure (RR=1.81, 95%CI 1.19–2.73; p=.005 for mmURD and RR=1.50, 95%CI 1.10–2.05; p=.011 for UCB) and overall mortality (RR=1.98, 95%CI 1.29–3.05; p=.002 for mmURD and RR=1.68, 95%CI 1.21–2.34; p=.002 for UCB). In addition, among the Ph+ subgroup, LFS after alloHCT was not associated with consolidation or MRD-positive status.

Acute and Chronic GVHD

The cumulative incidence of acute GVHD at day 100 for ≥2, 1, and 0 cycles of consolidation chemotherapy was 41%, 41%, and 37%, respectively (p=0.86). Similarly, the cumulative incidence of chronic GVHD at 1-year was 52%, 47%, and 48%, respectively (p=0.68). Consolidation chemotherapy was not associated with the incidence of GVHD; however, acute GVHD was influenced by graft source, and chronic GVHD was influenced by time to CR1, graft source, donor type, and *in vivo* T cell depletion. In multiple regression analysis, consolidation was not found to be an independent predictor of acute or chronic GVHD. In

contrast, well-matched URD (RR=1.45, 95%CI 1.05–2.01; p=.026) was associated with increased risk of acute GVHD as compared to HLA-identical sibling donor type, whereas *in vivo* T cell depletion (RR=0.55, 95%CI 0.38–0.80; p=.002) significantly reduced the risk of chronic GVHD.

DISCUSSION

We conducted a large analysis of CIBMTR data on 524 patients with ALL in CR1 to determine whether consolidation chemotherapy affected clinical outcomes of myeloablative alloHCT. We found that consolidation chemotherapy had no demonstrable benefit for myeloablative alloHCT recipients—an observation not previously reported. We observed similar rates of LFS, OS, relapse, and TRM in CR1 ALL patients independent of consolidation chemotherapy use. Since many ALL treatment protocols for adults still incorporate mandatory consolidation even for those undergoing alloHCT,[21] this observation has practical importance for clinicians because it suggests that consolidation is not necessary for those patients with readily available donors undergoing prompt myeloablative alloHCT for ALL in CR1, especially when a negative MRD status can be verified. On the other hand, our analysis showed that consolidation had no negative effect on TRM or survival after alloHCT. Because a previous report found that the time from induction chemotherapy to consolidation was independently associated with increased risk of relapse in ALL,[10] our data suggest that consolidation can be safely used to prevent leukemia relapse in those waiting for suitable donor without increasing the risk of TRM.

In this study, factors including patient age, comorbidities, Ph+ status, or WBC at diagnosis were not independently associated with clinical outcomes after alloHCT. In addition, exclusion of patients younger than 18 years (n=29) had no significant effect on any clinical outcomes after transplantation (data not shown). Notably, no consolidation group was enriched with older patients and patients with comorbidities. Although factors determining the choice of offering consolidation cannot be assessed in this retrospective study, older age and patient comorbidities are common reasons why consolidation might not be routinely administered in clinical practice. Despite this, however, in our study factors such as older age or comorbidities did not significantly increase the risk of TRM or mortality in patients receiving no consolidation.

Although the adverse influence of hyperleukocytosis[22–26] or CNS leukemia[27] on clinical outcomes of ALL were previously reported in several studies, this effect was not observed in our analysis. However, our study had only a smaller proportion of patients with hyperleukocytosis or CNS leukemia (<10% for each); therefore, the effect of these factors on transplant outcomes could not be robustly assessed. Despite the high proportion of Ph+ ALL cases (44%) in our study cohort, we observed no influence of Ph+ status on transplantation outcomes. Our observation is consistent with several prior reports of improved outcomes in myeloablative alloHCT recipients with Ph+ ALL.[28–32] The increased use of TKI maintenance before or after alloHCT in recent years might have influenced, in part, the improved outcomes of the otherwise well-known adverse subgroup with Ph+ ALL.[31–33]

Our study also highlights that achievement of CR1 with upfront therapy is an acceptable benchmark for disease control prior to myeloablative alloHCT. Several recent studies reported increased risk of ALL recurrence in patients undergoing alloHCT with positive MRD status using either flow cytometry or more sensitive polymerase chain reaction (PCR) molecular techniques,[34] particularly in a settings of reduced-intensity conditioning transplantation [31, 35–38] or myeloablative alloHCT in CR2.[39] In our analysis, MRD-positive status (though not quantitatively reported) among the Ph+ subgroup of patients had no influence on ALL relapse or LFS after transplantation. This observation is consistent with the UKALL XII/ECOG2993 results demonstrating that MRD-positive status had no adverse effect on outcomes of myeloablative alloHCT,[40] thereby emphasizing that myeloablative conditioning could potentially overcome the increased risk of relapse after transplantation of MRD-positive ALL in CR1. Although MRD status by high sensitivity flow cytometry assessment might differentially influence our observation, such information was not available for our analysis. However, we analyzed data on either cytogenetic or molecular MRD status in a majority of study patients and there was a similar distribution of detectable MRD cases among the three study groups. Future studies could reexamine the role of consolidation in flow cytometry detectable MRD to allow a better definition of whether such patients require consolidation prior to transplant to improve outcomes. At present, our study findings must only be cautiously extrapolated to cases with flow cytometry evidence of MRD and may not be applicable for patients undergoing reduced-intensity conditioning alloHCT.

These patients received various upfront ALL chemotherapy regimens and generally only “adult” type ALL therapy. More intense pediatric style intensification and consolidation therapy might alter this risk/benefit equation and in some subgoups might effectively substitute for the benefits of an allograft.[41]

These data support the conclusion that consolidation chemotherapy does not appear to provide added benefit in adult ALL patients who have an available donor permitting prompt initiation of myeloablative alloHCT in CR1. Consolidation should still be administrated to maintain CR1 prior to alloHCT in those awaiting donor availability.

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*Corporate Members

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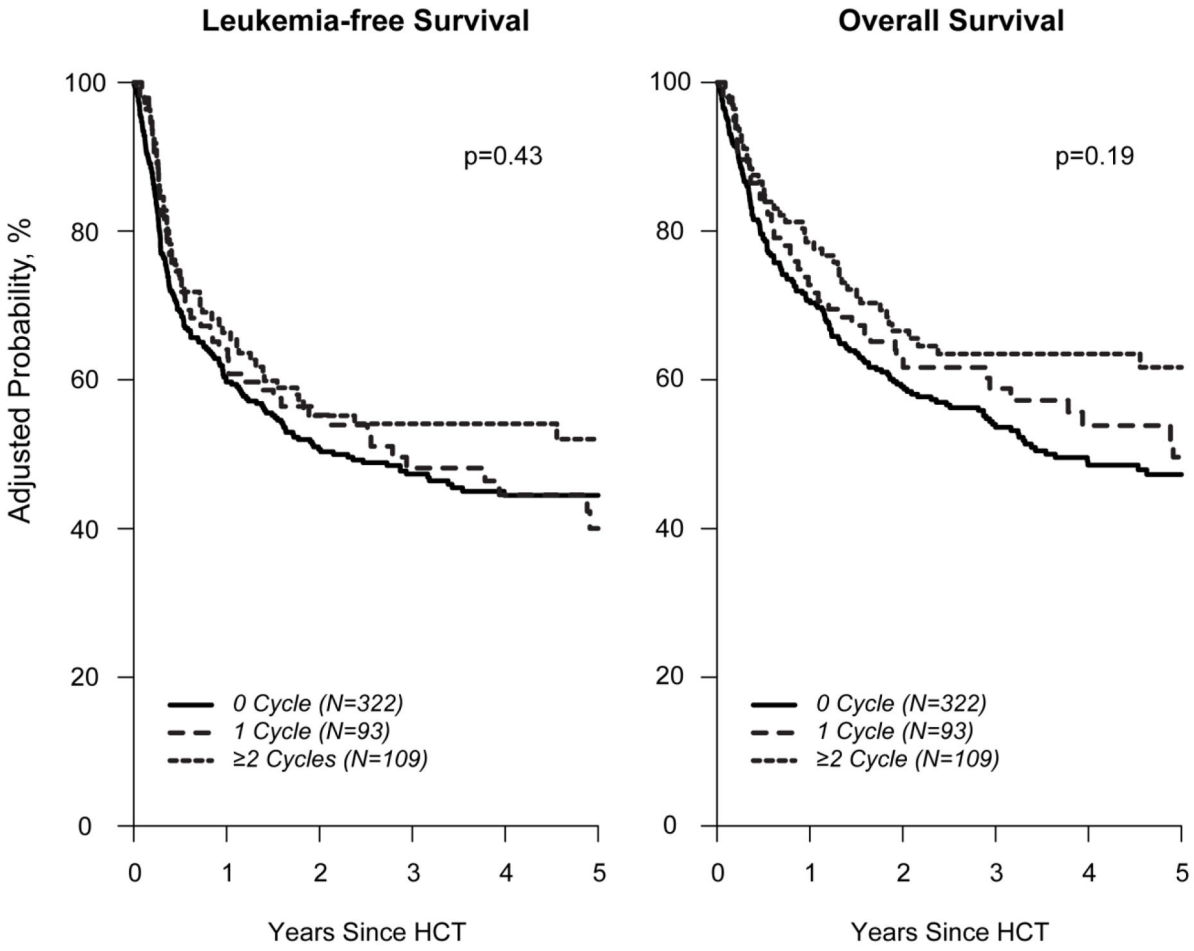
Highlights

- Consolidation prior to HCT does not appear to provide added benefit in CR1 ALL
- Pre-HCT consolidation in CR1 ALL is not prognostic for LFS or OS
- Pre-HCT consolidation in CR1 ALL does not influence the risk of relapse or TRM



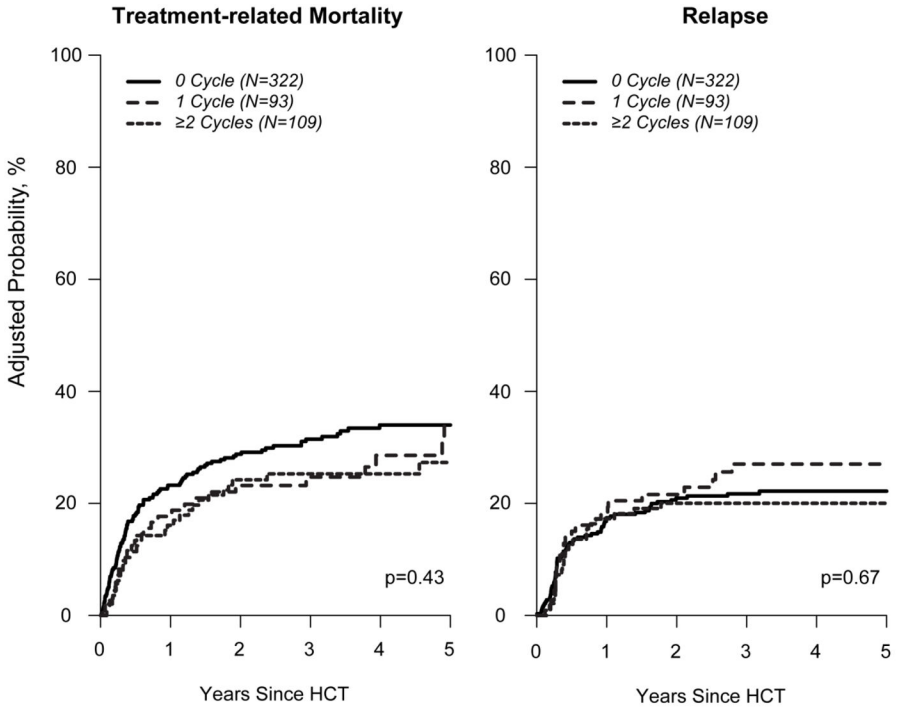


Figure 1.

Adjusted clinical outcomes of patients receiving ≥ 2, 1, or 0 cycles of consolidation chemotherapy prior to alloHCT.

Table 1

Patient Characteristics

	Consolidation Chemotherapy			
Variable	**0 cycles**	**1 cycle**	**≥2 cycles**	**P-value**
Number of patients	322	93	109	
Number of centers	89	45	62	
Age in decades				0.17
16–29	97 (30)	36 (39)	39 (36)	
30–39	62 (19)	16 (17)	30 (28)	
40–49	90 (28)	20 (22)	22 (20)	
50–59	62 (19)	16 (17)	17 (16)	
60–69	11 (3)	5 (5)	1 (<1)	
Median (range)	40 (16–68)	36 (17–67)	35 (16–65)	0.01
Gender				0.55
Male	191 (59)	51 (55)	59 (54)	
Female	131 (41)	42 (45)	50 (46)	
Karnofsky score				0.07
<90%	102 (32)	17 (18)	35 (32)	
≥90%	215 (67)	76 (82)	72 (66)	
Missing	5 (2)	0	2 (2)	
ALL immunophenotype				0.55
B-lineage	265 (82)	75 (81)	92 (84)	
T-lineage	51 (16)	14 (15)	13 (12)	
Missing	6 (2)	4 (4)	4 (4)	
White blood cell count at diagnosis				0.62
≤10	116 (36)	40 (43)	38 (35)	
10–29	43 (13)	8 (9)	10 (9)	
30 – 100	36 (11)	13 (14)	12 (11)	
>100	22 (7)	8 (9)	11 (10)	
Missing	105 (33)	24 (26)	38 (35)	
Median (range)	8 (<1–432)	8 (1–429)	8 (1–1410)	0.95
HCT-CI				0.04
0	191 (59)	64 (69)	61 (56)	
1–2	78 (24)	16 (17)	33 (30)	
≥3	52 (16)	10 (11)	14 (13)	
Missing	1 (<1)	3 (3)	1 (<1)	
Cytogenetics scoring[a]				0.30
Normal	72 (22)	18 (19)	22 (20)	
Poor	188 (58)	55 (59)	66 (61)	
Other	45 (14)	9 (10)	16 (15)	
Missing	17 (5)	11 (12)	5 (5)	
Philadelphia positive				0.22

	Consolidation Chemotherapy			
Variable	**0 cycles**	**1 cycle**	**≥2 cycles**	**P-value**
No	163 (51)	51 (55)	66 (61)	
Yes	153 (48)	38 (41)	40 (37)	
Missing	6 (2)	4 (4)	3 (3)	
Extramedullary disease at diagnosis				1.00
No	264 (82)	77 (83)	91 (83)	
Yes	48 (15)	13 (14)	15 (14)	
Missing	10 (3)	3 (3)	3 (3)	
Extramedullary or CNS leukemia at diagnosis				0.88
No	281 (87)	81 (87)	99 (91)	
Yes	31 (10)	9 (10)	7 (6)	
Missing	10 (3)	3 (3)	3 (3)	
Number of induction cycles				0.72
1	278 (86)	77 (83)	93 (85)	
2	30 (9)	14 (15)	11 (10)	
3	11 (3)	2 (2)	4 (4)	
4	3 (<1)	0	1 (<1)	
CNS prophylaxis[b]				0.005
No	96 (30)	18 (19)	17 (16)	
Yes	226 (70)	75 (81)	92 (84)	
Time from diagnosis to CR1				<0.001
0–2 months	136 (42)	61 (66)	80 (73)	
2–6 months	138 (43)	24 (26)	25 (23)	
≥6 months	28 (9)	3 (3)	2 (2)	
Missing	20 (6)	5 (5)	2 (2)	
Number of consolidation cycles				<0.001
0	322	0	0	
1	0	93	0	
2	0	0	59 (54)	
3	0	0	22 (20)	
4	0	0	17 (16)	
≥5	0	0	10 (9)	
Missing	0	0	1 (<1)	
Time from CR1 to HCT				<0.001
0–2 months	144 (45)	17 (18)	9 (8)	
2–4 months	89 (28)	44 (47)	33 (30)	
4–6 months	38 (12)	15 (16)	31 (28)	
≥6 months	31 (10)	12 (13)	34 (31)	
Missing	20 (6)	5 (5)	2 (2)	
Cytogenetic CR status at HCT (n=379; poor +other)				0.33
No	16 (7)	2 (3)	6 (7)	

	Consolidation Chemotherapy			
Variable	**0 cycles**	**1 cycle**	**≥2 cycles**	**P-value**
Yes	191 (82)	59 (92)	70 (85)	
Missing	26 (11)	3 (5)	6 (7)	
Molecular CR status at HCT (n=231; Ph+ patients only)				0.66
No	43 (28)	8 (21)	10 (25)	
Yes	77 (50)	24 (63)	20 (50)	
Missing	33 (22)	6 (16)	10 (25)	
TBI				0.63
No	26 (8)	8 (9)	6 (6)	
Yes	296 (92)	85 (91)	103 (94)	
<600 cGy	23	3	9	
600–1200 cGy	148	40	62	
>1200 cGy	125	42	32	
Conditioning regimen[c]				0.47
TBI + Cy	150 (47)	35 (38)	43 (39)	
TBI + Cy + other	75 (23)	20 (20)	32 (29)	
TBI + VP16	62 (19)	21 (23)	23 (21)	
TBI + other	15 (5)	11 (12)	9 (8)	
Bu + Cy	7 (2)	3 (3)	1 (<1)	
Bu + Flu	13 (4)	3 (3)	1 (<1)	
In-vivo T cell depletion				0.11
No	266 (83)	80 (86)	82 (75)	
Yes	56 (17)	13 (14)	27 (25)	
Type of donor				0.40
HLA-identical sibling	130 (40)	37 (40)	38 (35)	
Well matched URD	96 (30)	23 (25)	31 (28)	
Partially matched URD	22 (7)	10 (11)	10 (9)	
Mismatched URD	2 (<1)	1 (1)	3 (3)	
UCB	72 (23)	22 (23)	27 (25)	
6/6 UCB	5	1	0	
5/6 UCB	6	2	4	
≤4/6 UCB	31	4	11	
Matching unknown	30	15	12	
Graft type				0.42
Bone marrow	39 (12)	19 (20)	14 (13)	
Peripheral blood	211 (66)	52 (56)	68 (62)	
Single UCB	22 (7)	5 (5)	6 (6)	
Double UCB	50 (16)	17 (18)	21 (19)	
Donor/Recipient CMV match				0.05
−/−	92 (29)	16 (17)	39 (36)	
−/+	112 (35)	33 (35)	35 (32)	

	Consolidation Chemotherapy			
Variable	**0 cycles**	**1 cycle**	**≥2 cycles**	**P-value**
+/−	36 (11)	13 (14)	7 (6)	
+/+	81 (25)	31 (33)	24 (22)	
Missing	1 (<1)	0	4 (4)	
Donor/Recipient sex match				0.44
M/M	115 (36)	28 (30)	30 (28)	
M/F	73 (23)	28 (30)	21 (19)	
F/M	71 (22)	23 (25)	24 (22)	
F/F	52 (16)	14 (15)	26 (24)	
Double UCB w/ sex mismatch	11 (3)	0	8 (7)	
GVHD prophylaxis				0.16
Tacrolimus based	219 (68)	57 (61)	73 (67)	
Cyclosporine based	87 (27)	29 (31)	35 (32)	
Other	16 (5)	7 (8)	1 (<1)	
TKI maintenance (pre- or post-HCT) (n=231; Ph+ patients only)				0.10
No	82 (54)	17 (45)	14 (35)	
Yes	71 (46)	21 (55)	26 (65)	
Year of HCT				0.40
2008	97 (30)	28 (30)	33 (30)	
2009	65 (20)	20 (22)	27 (25)	
2010	56 (17)	15 (16)	13 (12)	
2011	67 (21)	13 (14)	17 (16)	
2012	37 (11)	17 (18)	19 (17)	
Median follow-up of survivors (range), months	50 (4–78)	61 (12–76)	52 (15–74)	

Table 2

Univariate analysis

	Consolidation Chemotherapy						
	0 cycles (N = 322)		1 cycle (N = 93)		≥2 cycles (N =109)		
Outcomes	**N**	**Probability (95% CI)**	**N**	**Probability (95% CI)**	**N**	**Probability (95% CI)**	**p-value**
aGVHD grade II-IV	321		93		109		0.86
100-day		37 (32–43)%		41 (31–51)%		41 (32–51)%	
cGVHD	321		93		109		0.68
1-year		48 (42–53)%		47 (36–57)%		52 (42–61)%	
3-year		56 (50–62)%		NE *		58 (48–67)%	
5-year		57 (51–62)%		NE *		NE *	
Relapse	321		92		109		0.71
1-year		17 (13–22)%		18 (11–27)%		17 (11–25)%	
3-year		21 (17–26)%		26 (17–36)%		20 (13–28)%	
5-year		22 (18–27)%		26 (17–36)%		20 (13–28)%	
Treatment related mortality	321		92		109		0.56
1-year		23 (18–28)%		18 (11–27)%		17 (10–24)%	
3-year		31 (26–36)%		26 (17–35)%		26 (18–35)%	
5-year		33 (28–39)%		34 (23–45)%		28 (19–37)%	
Leukemia-free survival	321		92		109		0.48
1-year		60 (55–65)%		63 (53–73)%		66 (57–75)%	
3-year		48 (42–53)%		48 (38–59)%		54 (44–63)%	
5-year		45 (39–50)%		40 (29–52)%		52 (42–62)%	
Overall survival	322		93		109		0.21
1-year		71 (66–76)%		72 (63–81)%		78 (70–85)%	
3-year		54 (49–60)%		58 (48–68)%		63 (53–72)%	
5-year		48 (42–54)%		49 (37–60)%		61 (51–70)%	

* NE, not evaluable, less than 15 cases at risk at specified time point

Table 3

Multivariable analysis

	N	RR* (95% CI)	p-value
1. acute GVHD II-IV			
Number of consolidation cycles			0.98
≥2 cycles	109	1	
0 cycles	322	0.97 (0.70–1.35)	0.87
1 cycle	93	0.96 (0.63–1.47)	0.85
Donor type			0.10
HLA-identical sibling	205	1	
Well matched URD	150	1.45 (1.05–2.01)	0.026
Partially/mismatched URD	48	1.41 (0.87–2.29)	0.17
UCB	121	1.42 (1.00–2.01)	0.053
Recipient age at HCT			0.36
16–39	280	1	
≥40	244	0.88 (0.67–1.16)	
2. chronic GVHD			
Number of consolidation cycles			0.59
≥2 cycles	109	1	
0 cycles	322	0.94 (0.70–1.26)	0.68
1 cycle	93	0.82 (0.56–1.20)	0.31
Donor type			0.082
HLA-identical sibling	205	1	
Well matched URD	150	1.01 (0.75–1.36)	0.96
Partially/mismatched URD	48	1.42 (0.87–2.31)	0.16
UCB	121	0.74 (0.53–1.02)	0.066
In-vivo T-cell depletion			0.0019
No	428	1	
Yes	96	0.55 (0.38–0.80)	
Recipient age at HCT			0.57
16–39	280	1	
≥40	244	0.93 (0.74–1.18)	
3. Treatment related mortality			
Number of consolidation cycles			0.43
≥2 cycles	109	1	
0 cycles	322	1.30 (0.86–1.96)	0.22
1 cycle	93	1.12 (0.66–1.91)	0.67
Donor type			<.0001
HLA-identical sibling	205	1	
Well matched URD	150	1.33 (0.87–2.04)	0.19

	N	RR* (95% CI)	p-value
Partially/mismatched URD	48	3.11 (1.87–5.18)	<.0001
UCB	121	2.46 (1.64–3.71)	<.0001
Recipient age at HCT			0.10
16–39	280	1	
≥40	244	1.31 (0.95–1.81)	
HCT-CI			0.56
0	316	1	
1	75	1.06 (0.65–1.74)	0.80
≥2	128	1.22 (0.85–1.76)	0.28
4. Relapse			
Number of consolidation cycles			0.67
≥2 cycles	109	1	
0 cycles	322	1.15 (0.71–1.87)	0.57
1 cycle	93	1.31 (0.73–2.34)	0.37
Donor type			0.63
HLA-identical sibling	205	1	
Well matched URD	150	0.92 (0.60–1.42)	0.71
Partially/mismatched URD	48	0.81 (0.38–1.70)	0.57
UCB	121	0.71 (0.42–1.21)	0.21
Recipient age at HCT			0.80
16–39	280	1	
≥40	244	0.95 (0.66–1.38)	
5. Treatment failure (1 - LFS)			
Number of consolidation cycles			0.43
≥2 cycles	109	1	
0 cycles	322	1.23 (0.90–1.69)	0.19
1 cycle	93	1.19 (0.80–1.77)	0.38
Donor type			0.0096
HLA-identical sibling	205	1	
Well matched URD	150	1.11 (0.82–1.51)	0.48
Partially/mismatched URD	48	1.81 (1.19–2.73)	0.0051
UCB	121	1.50 (1.10–2.05)	0.011
Recipient age at HCT			0.22
16–39	280	1	
≥40	244	1.16 (0.91–1.49)	
HCT-CI			0.56
0	316	1	
1	75	1.13 (0.80–1.60)	0.50
≥2	128	1.07 (0.81–1.43)	0.63
6. Overall mortality (1 - OS)			

	N	RR* (95% CI)	p-value
Number of consolidation cycles			0.19
≥2 cycles	109	1	
0 cycles	322	1.38 (0.98–1.94)	0.065
1 cycle	93	1.31 (0.85–2.00)	0.22
Donor type			0.0015
HLA-identical sibling	205	1	
Well matched URD	150	1.14 (0.83–1.57)	0.43
Partially/mismatched URD	48	1.98 (1.29–3.05)	0.0019
UCB	121	1.68 (1.21–2.34)	0.0020
Recipient age at HCT			0.14
16–39	280	1	
≥40	244	1.22 (0.94–1.58)	
HCT-CI			0.16
0	316	1	
1	75	1.22 (0.85–1.76)	0.29
≥2	128	1.22 (0.90–1.65)	0.19
7. Relapse (Ph+ subset)			
Number of consolidation cycles			0.75
≥2 cycles	40	1	
0 cycles	153	1.05 (0.47–2.35)	0.91
1 cycle	38	1.35 (0.54–3.40)	0.53
Donor type			0.46
HLA-identical sibling	87	1	
Well matched URD	65	0.74 (0.37–1.48)	0.39
Partially/mismatched URD	21	0.96 (0.35–2.61)	0.94
UCB	58	0.53 (0.24–1.20)	0.13
Recipient age at HCT			0.073
16–39	99	1	
≥40	132	0.59 (0.33–1.05)	
MRD status			0.84
No	115	1	
Yes	67	1.21 (0.63–2.32)	0.57
Missing	49	1.14 (0.52–2.49)	0.74
8. Overall mortality (Ph+ subset)			
Number of consolidation cycles			0.84
≥2 cycles	40	1	
0 cycles	153	1.04 (0.64–1.70)	0.86
1 cycle	38	0.89 (0.48–1.67)	0.73
Donor type			0.64
HLA-identical sibling	87	1	

	N	RR* (95% CI)	p-value
Well matched URD	65	1.22 (0.78–1.90)	0.38
Partially/mismatched URD	21	1.35 (0.68–2.67)	0.39
UCB	58	1.27 (0.80–2.02)	0.30
Recipient age at HCT			0.68
16–39	99	1	
≥40	132	1.08 (0.75–1.57)	
MRD status			0.56
No	115	1	
Yes	67	1.02 (0.67–1.57)	0.92
Missing	49	1.27 (0.80–2.02)	0.31
HCT-CI			0.45
0	140	1	
1	30	0.96 (0.54–1.69)	0.89
≥2	59	1.19 (0.79–1.78)	0.41