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Evaluation of Allogeneic Transplantation in First or Later Minimal Residual Disease-Negative Remission Following Adult-Inspired Therapy for Acute Lymphoblastic Leukemia

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Abstract

Comparisons without hematopoietic cell transplantation (HCT) to myeloablative (MAC) or reduced-intensity HCT (RIC) for adults with acute lymphoblastic leukemia (ALL) in first minimal-residual-disease negative remission (MRD^{Neg} CR1) are limited. Further, the importance of MRD^{Neg} following salvage therapy (MRD^{Neg} CR2+) is unknown. We evaluated 89 patients in MRD^{Neg} CR1 after adult-inspired treatment: 33 received MAC (12 Philadelphia chromosome [Ph] +), 17 received RIC (13 Ph+), and 39 Deferred HCT (3 Ph+). 3-year overall survival (OS) estimates for MAC, RIC, and Deferred HCT were 71%, 69%, and 68%, while 3-year event-free survival (EFS) estimates were 65%, 54%, and 28%, respectively. Further, HCT in MRD^{Neg} CR1 performed similarly to MRD^{Neg} CR2+: 3-year OS estimates were 70% and 69%, and 3-year EFS estimates were 62% and 62%, respectively. In conclusion, adults with ALL in MRD^{Neg} CR1 following adult-inspired therapy had similar OS with or without HCT, and HCT in MRD^{Neg} CR2+ can yield long-term survival.

Keywords

neoplasia – lymphoid leukemia; marrow and stem cell transplantation – clinical results; neoplasia – chemotherapeutic approaches; neoplasia – prognostication

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Conflict of Interest Statement

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Introduction

Allogeneic hematopoietic cell transplantation (HCT) with myeloablative conditioning (MAC) improves overall survival (OS) in adults with acute lymphoblastic leukemia (ALL) in first remission.¹⁻³ This benefit, however, is relatively modest when employed in unselected patients, with the risk of non-relapse mortality (NRM) negating much of the benefits observed in relapse risk reduction. Furthermore, the risk of NRM after MAC can be prohibitive.⁴ This has led to the use of non-myeloablative and reduced-intensity conditioning (RIC) regimens, particularly for use in this patient population.^{5,6} RIC yields comparable results to MAC based on registry data,^{7,8} though the best results with RIC are seen in patients without minimal residual disease (MRD) prior to HCT.^{5,9}

MRD is arguably the most important prognostic and predictive factor in ALL.¹⁰ Its presence or absence can supersede historical clinical risk factors, such as age, cytogenetics, and white blood cell count (WBC) at presentation;¹¹⁻¹³ as a result, these factors are likely less important once patients achieve MRD negativity (MRD^{Neg}). Patients that are MRD^{Neg} have superior outcomes to those who are MRD positive (MRD^{Pos}) after undergoing either MAC or RIC.^{9,14,15} Further, MRD^{Neg} also predicts superior outcomes with chemotherapy alone without the use of HCT (No HCT).^{11,16,17} However, to date, comparisons of HCT and non-HCT approaches for adults with ALL in first MRD^{Neg} remission (MRD^{Neg} CR1) are limited: HCT following pediatric-inspired front-line therapy may not offer much benefit,¹⁸ but no such comparisons exist with adult-inspired treatment.

Also, little is known about the importance of MRD in the setting of salvage therapy for those who relapse. Historically, outcomes for adults with relapsed/refractory ALL are poor, even with HCT.^{19,20} New agents in development will hopefully change the landscape of this very challenging problem, with promising response rates in single-agent studies.²¹⁻²³ Whether these responses will translate into better long-term remissions remains to be seen; currently HCT remains the only intervention with established curative potential for adults with relapsed/refractory ALL.

To provide insight into these questions, we reviewed our institution's experience treating adults with ALL. We hypothesized that patients in MRD^{Neg} CR1 following adult-inspired treatment would have similar outcomes with or without HCT in CR1. If correct, this would support MRD as an effective biomarker to identify patients who are less likely to benefit from HCT in CR1 following adult-based treatment. Further, we hypothesized that HCT remains an effective option for patients who relapse, provided they can achieve a later MRD^{Neg} remission (MRD^{Neg} CR2+). This finding would advance HCT as a goal for patients with relapsed/refractory disease, particularly as options to achieve deep remissions in these patients improve.

Materials and Methods

PATIENT SELECTION

Records from consecutive patients older than 18 years with ALL who received care at our Center between January 2005 and December 2013 were reviewed. Patients with isolated

extramedullary disease (i.e., no marrow involvement) or Burkitt lymphoma/leukemia were excluded. All patients who were treated on an investigational study provided informed consent in accordance with the Declaration of Helsinki. Separate institutional approval was obtained for this analysis to retrospectively review patient records.

CLINICAL DATA COLLECTION AND DEFINITIONS

Clinical characteristics were obtained from all patients, where available. Only patients who had an assessment for MRD within 3 months of starting treatment were included. High-risk clinical features were defined as age at diagnosis of over 35 years, high WBC at diagnosis ($>30,000/\mu\text{L}$ for B-cell ALL, $>100,000/\mu\text{L}$ for T-cell ALL), and adverse cytogenetics identified either by metaphase analysis or fluorescence *in situ* hybridization (FISH). Specifically, the following abnormalities were defined as high-risk, as reported previously: t(9;22) or the Philadelphia chromosome (Ph+); rearrangements involving *MLL* on 11q23; complex karyotype (i.e., 5 or more structural or numerical abnormalities), low hypodiploidy, near triploidy, monosomy 7, and trisomy 8.²⁴⁻²⁶ Decisions regarding the specifics of treatment and referral for allogeneic HCT were not prospectively assigned and were left to the opinion of the treating physicians.

DEFINITION OF RESPONSE ASSESSMENTS AND MRD

All response assessments were based on evaluation of bone marrow examinations. The timing and nature of response assessments were left to the discretion of the treating physicians. MRD^{Neg} was defined as no evidence of quantifiably detectable disease by all measures utilized (i.e., morphology, multi-parameter flow cytometry [MFC], cytogenetics, FISH, and/or polymerase chain reaction [PCR]). Though these assays were not all uniformly applied to all assessments, MFC was used in all patients. The MFC platform used in our laboratory at the University of Washington (UW) has a sensitivity of 0.01-0.001%, depending on background populations.²⁷ However, MFC data from other laboratories were included when utilized. Patients were only considered to have achieved MRD^{Neg} CR1 if they received 1 line of therapy to become MRD^{Neg}. Furthermore, because of the high risk of morphologic relapse associated with recurrence of MRD,²⁸ relapse was defined as either morphologic (i.e., $> 5\%$ bone marrow blasts) recurrence or MRD reappearance,²⁹ except when MRD reappearance occurred transiently within the first 3 months after HCT.

STATISTICAL ANALYSIS

Patients were entered into the risk set for this analysis when they achieved an MRD^{Neg} remission. Since the time to MRD^{Neg} relative to the time of diagnosis, treatment initiation, and HCT varies, a uniform “time zero” cannot be precisely defined. Therefore, MAC, RIC, and Deferred HCT groups were treated as time-dependent covariates with left truncation.³⁰ When events (i.e., death, relapse, and/or secondary malignancy) occurred, they were credited to whichever group the patient was in at that time. Frequencies of characteristics were compared between groups using a Fisher’s exact test. Kaplan-Meier curves were used to estimate the probabilities of OS and event-free survival (EFS), where an event was defined as relapse or death. The statistical significance of differences in event rates was evaluated with Cox proportional hazards regression models. Adjustments to these models were made using covariates with known prognostic significance where possible.

Results

PATIENT CHARACTERISTICS: MRD^{NEG} WITH ADULT-INSPIRED TREATMENT

Out of a total of 187 patients, 89 (48%) had MRD assessed 3 months from starting adult-inspired treatment and, during the course of this initial treatment, achieved an MRD^{Neg} remission. These patients were significantly less likely to suffer an event (53%) than the 53 patients with persistent MRD (75%; $p = 0.008$). The median time from initiation of therapy to documented MRD^{Neg} CR1 was 1.6 months (range = 0.23-9.8 months): 27% ($n = 24$) achieved MRD^{Neg} CR1 within 1 month, 72% ($n = 64$) within 3 months, and 98% ($n = 87$) within 6 months. Of these 89 MRD^{Neg} patients, 33 (37%) underwent MAC, 17 (19%) underwent RIC, and 39 (44%) did not undergo HCT in CR1 (Figure 1). Initial therapy began in the following ranges for these 3 groups: March 2005-December 2013 for MAC, March 2005-November 2013 for RIC, and October 2006-March 2014 for Deferred HCT.

The characteristics of these groups are summarized and compared in Table I. Patients in the RIC group were more likely to have high-risk cytogenetics ($p = 0.002$), which was exclusively due to Ph+. Age was also generally higher in the RIC group, but not to a significantly different degree ($p = 0.061$). There were no significant differences in the initial treatment given: the majority in all 3 groups received hyperCVAD,³¹ while the Larson³² and Linker regimens³³ were used less often. Rituximab was added to hyperCVAD in 13 patients (19% treated with this regimen). All patients with Ph+ ALL received either imatinib or dasatinib with their initial treatment. All patients in the MAC group received high-dose total body irradiation (TBI)-based conditioning, while all in the RIC group were given fludarabine and low-dose TBI. Patients who did not undergo HCT in MRD^{Neg} CR1 received maintenance therapy at the discretion of the treating physicians. The median follow-up from the time of diagnosis for all surviving patients was 42 months (range = 4-113 months).

COMPARISON OF OUTCOMES: MAC VS RIC VS NO HCT IN MRD^{NEG} CR1

Using a Cox proportional hazards model with left truncation adjusted for WBC, there were no statistically significant differences in either OS or EFS between MAC, RIC, or Deferred HCT in MRD^{Neg} CR1; however, relapse was less likely with both MAC and RIC (Table II). A relatively similar pattern is observed when looking at Ph+ and patients without an identified Philadelphia chromosome (Ph-) separately (Table II). Models in the Ph- subgroup were adjusted for WBC, but no adjustments were possible in the Ph+ subgroup due to an insufficient number of events. Due to the comparable outcomes between MAC and RIC and the small number of patients in each subgroup, patients who underwent HCT in MRD^{Neg} CR1 were grouped together for this analysis. That said, there were 4 patients in the RIC group that were Ph-, and none had experienced an event across a median of 38 months (range = 26-53 months) from HCT.

Kaplan-Meier curves depicting OS, EFS, and cumulative incidence of relapse (CIR) are shown in Figure 2. As stated previously, it is difficult to assign a “time zero” that applies fairly across these 3 groups. Thus, it is inappropriate to make formal statistical comparisons between the HCT and Deferred HCT groups using Kaplan-Meier analyses, where a uniform “time zero” is required. Therefore, MAC and RIC are compared relative to their date of HCT

(Figure 2A, C, and E), whereas the Deferred HCT group is plotted separately and relative to the date that MRD^{Neg} CR1 was first documented (Figure 2B, D, and F). Relative to the initiation of therapy, the median time to MRD^{Neg} remission in the Deferred HCT group was 1.4 months (range = 0.4-9.8 months), while the median time to HCT for the MAC and RIC groups were 6.2 months (range = 3.3-18.2 months) and 6.6 months (range = 3.7-19.0 months), respectively.

For patients in MRD^{Neg} CR1, there was no difference in either EFS or OS between the MAC and RIC groups, though CIR was significantly higher following RIC ($p = 0.04$). In Cox proportional hazard models adjusted for age at diagnosis, the HR for OS with MAC was 2.6 (95% CI = 0.60-11.0; $p = 0.21$; 17 events) when compared to RIC, while the HR for EFS was 1.42 (95% CI = 0.41-5.0; $p = 0.58$; 21 events). The OS in the Deferred HCT group appears to be comparable to those who did receive HCT. However, EFS and CIR appear to be less favorable in this group. This is demonstrated in Table III, which shows time-to-event analyses for all 3 groups.

Because of the higher risk of relapse for patients in the Deferred HCT group, we examined the outcomes of these 39 patients in greater detail. Relapse was observed in 25 patients (64%), a median of 6 months (range = 0.5-49 months) after achieving MRD^{Neg} CR1, while the remainder are alive and in remission a median of 15 months (range = 4-73 months) from their initial diagnosis. Among the 25 patients who relapsed, 10 (40%) did so either in the midst of initial therapy or prior to planned HCT in MRD^{Neg} CR1, 7 (28%) were felt to be at sufficiently low risk of relapse that HCT was not recommended in CR1, and 2 (8%) did not have a suitable donor available while in MRD^{Neg} CR1; HCT was deferred in the remaining 6 patients for miscellaneous reasons (e.g., patient declined). Ultimately, however, 22 patients (88%) were able to undergo salvage HCT, 13 (59%) of whom were in an MRD^{Neg} remission at the time of HCT. Therapies used following relapse included hyperCVAD ($n = 10$), Linker ($n = 5$), nelarabine ($n = 4$), and high-dose cytarabine plus mitoxantrone (HAM; $n = 1$); 4 patients went directly to HCT after MRD reappearance; and 1 patient was lost to follow-up following recurrence. Relapse after salvage HCT occurred in 7 patients, 2 among those who were MRD^{Neg} at HCT (15%) and 5 among those who were MRD^{Pos} at HCT (55%; $p = 0.074$). The 3 (12%) patients that did not undergo salvage HCT have since died.

COMPARISON OF OUTCOMES: HCT IN MRD^{NEG} CR1 VS MRD^{NEG} CR2+

To evaluate the importance of MRD status beyond first remission, we evaluated our full population of 187 patients, of whom 50 patients (33 from the MAC group and 17 from the RIC group) underwent HCT in MRD^{Neg} CR1 and 20 patients underwent HCT in MRD^{Neg} CR2+. This group included the 13 patients (65%) mentioned above who achieved an MRD^{Neg} CR1 but subsequently relapsed after not undergoing HCT in CR1. It also included an additional 7 patients (35%) who did not achieve an MRD^{Neg} remission with their initial therapy, but did subsequently after receiving salvage therapy. Of importance, the rate of achieving MRD^{Neg} CR2+ after having been in MRD^{Neg} CR1 without HCT (52%) is significantly higher than that observed in patients who were unable to achieve MRD negativity with their initial therapy (13%; $p < 0.001$).

A comparison of the characteristics of these patients is depicted in Table IV. Similar to above, those referred for HCT while in MRD^{Neg} CR1 were significantly older ($p = 0.012$) and were more likely to have Ph+ disease ($p = 0.003$). While RIC was used in 34% of the transplants performed in MRD^{Neg} CR1, only 1 patient (5%) received such a treatment in MRD^{Neg} CR2+ ($p = 0.014$). Umbilical cord blood was used more frequently (25%) for those who underwent HCT in MRD^{Neg} CR2 compared to those in CR1 (4%; $p = 0.039$).

As shown in Figure 3, there were no significant differences in outcomes for patients who received HCT in MRD^{Neg} CR1 vs MRD^{Neg} CR2+, when compared relative to the date of HCT. The 3-year OS estimates were 70% after HCT in MRD^{Neg} CR1 vs 69% in HCT in MRD^{Neg} CR2+ ($p = 0.93$), while the median OS was 4.8 years and 5.2 years (respectively). For EFS, the 3-year estimates were 62% and 62% (respectively; $p = 0.60$), and the medians were 3.6 years and not reached (respectively). The 3-year estimates for CIR were 19% and 28% (respectively; $p = 0.60$), while the 1-year estimates for cumulative incidences of NRM were 19% and 15% (respectively; $p = 0.59$). In Cox proportional hazards models adjusted for age, the HR for OS following HCT in MRD^{Neg} CR2+ when compared to HCT in MRD^{Neg} CR1 was 1.06 (95% CI = 0.37-3.01; $p = 0.91$; 24 events), the HR for EFS was 0.95 (95% CI = 0.36-2.52; $p = 0.92$; 28 events), the HR for relapse was 2.01 (95% CI = 0.60-6.71; $p = 0.25$; 17 events), and the HR for NRM was 0.69 (95% CI = 0.16-2.89; $p = 0.61$; 13 events).

Discussion

Since the findings of the UKALL XII/ECOG2993 study demonstrated superior OS for adults with ALL who received HCT with MAC in CR1,¹ this has become a standard option for treatment of this disease. However, as our knowledge of response assessments and risk stratification has improved, the routine use of HCT for eligible adults with ALL in CR1 is no longer as clear. A practical method to determine the appropriate timing of this aggressive intervention is critical to optimize treatment approaches. Certainly, MRD assessment is at the forefront of this debate. While our results should be corroborated in an independent and prospective fashion before being used to make generalizable treatment decisions, they do provide several important observations.

The direct comparison of HCT and adult-inspired non-HCT approaches for patients who are MRD^{Neg} makes this analysis unique. While several prior studies have included patients who received either chemotherapy alone or consolidative HCT while in MRD^{Neg} CR1, the presence or absence of MRD often dictated this decision: patients who were MRD^{Neg} were not subjected to HCT in first remission, whereas those with persistent MRD were referred for HCT to improve the expected poor outcomes with chemotherapy alone.^{11,12} Studies such as this, while critical to the understanding of prospective treatment of adults with ALL, are not truly fair comparisons of how HCT performs compared to chemotherapy alone given the inherent selection bias. There have also been two recent *post hoc* or retrospective comparisons of pediatric-inspired initial therapy for Ph- disease followed with or without MAC, both of which suggest no benefit to HCT in CR1.^{18,34} Unlike these studies, our analysis looked exclusively at adult-inspired initial therapy (with the most commonly used being hyperCVAD), as well as Ph+ ALL and the potential role of RIC.

Another novel finding from our work is the comparable outcomes with HCT for patients in MRD^{Neg} CR1 vs MRD^{Neg} CR2+. A previous analysis of our Center's experience with MAC in ALL found that adjusting for CR status (i.e., CR1 vs CR2+) had no significant impact on the importance of MRD status.¹⁴ Our data suggest that the historically poor outcomes observed in adults with relapsed/refractory ALL are likely a consequence of ineffective salvage therapies and not a failure of HCT. Further, achieving MRD negativity with initial therapy appears to be predictive of subsequent sensitivity to salvage therapy (should relapse ultimately occur), with 59% achieving MRD^{Neg} CR2+. Having reached MRD^{Neg} CR1 suggests inherently chemotherapy-sensitive disease, so achieving MRD^{Neg} CR2+ is relatively likely if relapse occurs. This also explains why relatively inferior EFS and CIR did not translate into an inferior OS in the Deferred HCT group. However, it is worth emphasizing that achieving MRD^{Neg} in the salvage setting is not assured in the event of relapse following MRD^{Neg} CR1.

This retrospective analysis has a number of noteworthy limitations. First, the sample size is relatively small. With only 17 patients receiving RIC and the majority of them being Ph+, it is difficult to say how this approach fared compared to MAC or Deferred HCT. Suffice it to say, given the comparable outcomes in these groups as well as similar findings reported by CIBMTR,⁹ RIC would appear to be a reasonable option for adults with Ph+ ALL in MRD^{Neg} CR1. Next, while these patients were treated in a relatively contemporary era, we do not have data regarding oncogenetic status or molecular profiling, which may provide additional important prognostic/predictive information.^{13,35} Further, we currently do not have any data on the impact of co-morbidities, graft vs host disease, or quality of life.

Because of the heterogeneous manner in which response assessments were performed, we encountered other issues. We were limited to the analyses ordered by the treating physicians. This likely explains why a small proportion of patients were not recognized as achieving MRD^{Neg} CR1 until relatively late (i.e., 2% beyond 6 months) into their initial treatment. Second, direct comparisons of the groups were less straight-forward. That said, we used established statistical methods (i.e., Cox proportional hazard models with left truncation³⁰) to account for this. Related to this, there was an approximately 4-5 months difference from the time of treatment initiation to MRD^{Neg} confirmation in the Deferred HCT group compared to the time of treatment initiation to HCT in the MAC and RIC groups. This could introduce bias in favor of the HCT groups: patients needed to survive and stay in remission longer to enter these groups; relapse or death during that interval was scored as an event in the Deferred HCT group.

This analysis also suffers from several sources of referral bias. Patients with higher-risk clinical features were referred for HCT more often. However, as stated previously, it is not clear what (if any) impact these factors have in patients that are MRD^{Neg},¹⁰⁻¹³ and much of this difference was from older Ph+ patients being referred for RIC. Alternatively, older and/or more medically-infirm patients may not be referred for HCT. While the RIC group generally had older patients, the patients in the highest age ranges were in the Deferred HCT group (Table I). Additionally, we could only account for patients who were seen or treated at our Center. Thus, patients treated in the surrounding community who achieved MRD^{Neg} CR1 without the intent of HCT and never subsequently relapsed are unlikely to be referred

to our Center. More likely, we would see such patients to facilitate HCT while in MRD^{Neg} CR1 or after relapse, the latter of which further accounts for the inferior EFS and CIR observed in the Deferred HCT group. Overall, it would appear that these biases would generally seem to favor the HCT groups, yet the outcomes observed still were no different.

In conclusion, our findings corroborate those of other groups regarding the importance of MRD in the management of ALL. More distinctively, however, for patients who achieve an MRD^{Neg} remission with adult-inspired therapy (particularly hyperCVAD), the use of HCT in CR1 does appear to reduce the likelihood of relapse, but without significant improvement of OS. Patients in MRD^{Neg} CR1 who do not undergo HCT up-front also appear to be significantly more likely to achieve MRD^{Neg} CR2+ should they relapse, following which outcomes with HCT (primarily using MAC) are very similar to those who undergo HCT in MRD^{Neg} CR1. These findings have important ramifications, not only for the front-line risk stratification of adults with ALL but also for the evolving treatment landscape of treating relapsed/refractory ALL. As novel and more efficacious treatments are developed and methods of MRD detection improve, this may further advocate for reserving HCT as more of a salvage strategy for selected patients with ALL, much as it is currently used in the pediatric population and for other lymphoid malignancies.

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References

1. Goldstone AH, Richards SM, Lazarus HM, et al. In adults with standard-risk acute lymphoblastic leukemia, the greatest benefit is achieved from a matched sibling allogeneic transplantation in first complete remission, and an autologous transplantation is less effective than conventional consolidation/maintenance chemotherapy in all patients: final results of the International ALL Trial (MRC UKALL XII/ECOG E2993). *Blood*. 2008; 111(4):1827–1833. [PubMed: 18048644]
2. Cornelissen JJ, van der Holt B, Verhoef GE, et al. Myeloablative allogeneic versus autologous stem cell transplantation in adult patients with acute lymphoblastic leukemia in first remission: a prospective sibling donor versus no-donor comparison. *Blood*. 2009; 113(6):1375–1382. [PubMed: 18988865]
3. Ram R, Gafter-Gvili A, Vidal L, et al. Management of adult patients with acute lymphoblastic leukemia in first complete remission: systematic review and meta-analysis. *Cancer*. 2010; 116(14): 3447–3457. [PubMed: 20564092]
4. Sorrow ML, Maris MB, Storb R, et al. Hematopoietic cell transplantation (HCT)-specific comorbidity index: a new tool for risk assessment before allogeneic HCT. *Blood*. 2005; 106(8): 2912–2919. [PubMed: 15994282]
5. Ram R, Storb R, Sandmaier BM, et al. Non-myeloablative conditioning with allogeneic hematopoietic cell transplantation for the treatment of high-risk acute lymphoblastic leukemia. *Haematologica*. 2011; 96(8):1113–1120. [PubMed: 21508120]
6. Stein AS, Palmer JM, O'Donnell MR, et al. Reduced-intensity conditioning followed by peripheral blood stem cell transplantation for adult patients with high-risk acute lymphoblastic leukemia. *Biol Blood Marrow Transplant*. 2009; 15(11):1407–1414. [PubMed: 19822300]
7. Marks DI, Wang T, Perez WS, et al. The outcome of full-intensity and reduced-intensity conditioning matched sibling or unrelated donor transplantation in adults with Philadelphia

- chromosome-negative acute lymphoblastic leukemia in first and second complete remission. *Blood*. 2010; 116(3):366–374. [PubMed: 20404137]
8. Mohty M, Labopin M, Volin L, et al. Reduced-intensity versus conventional myeloablative conditioning allogeneic stem cell transplantation for patients with acute lymphoblastic leukemia: a retrospective study from the European Group for Blood and Marrow Transplantation. *Blood*. 2010; 116(22):4439–4443. [PubMed: 20716774]
 9. Bachanova V, Marks DI, Zhang MJ, et al. Ph+ ALL patients in first complete remission have similar survival after reduced intensity and myeloablative allogeneic transplantation: impact of tyrosine kinase inhibitor and minimal residual disease. *Leukemia*. 2014; 28(3):658–665. [PubMed: 23989431]
 10. Bruggemann M, Raff T, Kneba M. Has MRD monitoring superseded other prognostic factors in adult ALL? *Blood*. 2012; 120(23):4470–4481. [PubMed: 23033265]
 11. Bassan R, Spinelli O, Oldani E, et al. Improved risk classification for risk-specific therapy based on the molecular study of minimal residual disease (MRD) in adult acute lymphoblastic leukemia (ALL). *Blood*. 2009; 113(18):4153–4162. [PubMed: 19141862]
 12. Ribera JM, Oriol A, Morgades M, et al. Treatment of high-risk Philadelphia chromosome-negative acute lymphoblastic leukemia in adolescents and adults according to early cytologic response and minimal residual disease after consolidation assessed by flow cytometry: final results of the PETHEMA ALL-AR-03 trial. *J Clin Oncol*. 2014; 32(15):1595–1604. [PubMed: 24752047]
 13. Beldjord K, Chevret S, Asnafi V, et al. Oncogenetics and minimal residual disease are independent outcome predictors in adult patients with acute lymphoblastic leukemia. *Blood*. 2014; 123(24):3739–3749. [PubMed: 24740809]
 14. Bar M, Wood BL, Radich JP, et al. Impact of minimal residual disease, detected by flow cytometry, on outcome of myeloablative hematopoietic cell transplantation for acute lymphoblastic leukemia. *Leuk Res Treatment*. Prepublished on 23 March, 2014, as 10.1155/2014/421723.
 15. Zhou Y, Slack R, Jorgensen JL, et al. The effect of peritransplant minimal residual disease in adults with acute lymphoblastic leukemia undergoing allogeneic hematopoietic stem cell transplantation. *Clin Lymphoma Myeloma Leuk*. 2014; 14(4):319–326. [PubMed: 24548609]
 16. Gokbuget N, Kneba M, Raff T, et al. Adult patients with acute lymphoblastic leukemia and molecular failure display a poor prognosis and are candidates for stem cell transplantation and targeted therapies. *Blood*. 2012; 120(9):1868–1876. [PubMed: 22442346]
 17. Ravandi F, Jorgensen JL, Thomas DA, et al. Detection of MRD may predict the outcome of patients with Philadelphia chromosome-positive ALL treated with tyrosine kinase inhibitors plus chemotherapy. *Blood*. 2013; 122(7):1214–1221. [PubMed: 23836561]
 18. Dhedin N, Huynh A, Maury S, et al. Role of allogeneic stem cell transplantation in adult patients with Ph-negative acute lymphoblastic leukemia. *Blood*. 2015; 125(16):2486–2496. [PubMed: 25587040]
 19. Fielding AK, Richards SM, Chopra R, et al. Outcome of 609 adults after relapse of acute lymphoblastic leukemia (ALL); an MRC UKALL12/ECOG 2993 study. *Blood*. 2007; 109(3):944–950. [PubMed: 17032921]
 20. Kantarjian HM, Thomas D, Ravandi F, et al. Defining the course and prognosis of adults with acute lymphocytic leukemia in first salvage after induction failure or short first remission duration. *Cancer*. 2010; 116(24):5568–5574. [PubMed: 20737576]
 21. Kantarjian H, Thomas D, Jorgensen J, et al. Inotuzumab ozogamicin, an anti-CD22-calcitriol conjugate, for refractory and relapsed acute lymphocytic leukaemia: a phase 2 study. *Lancet Oncol*. 2012; 13(4):403–411. [PubMed: 22357140]
 22. Maude SL, Frey N, Shaw PA, et al. Chimeric antigen receptor T cells for sustained remissions in leukemia. *N Engl J Med*. 2014; 371(16):1507–1517. [PubMed: 25317870]
 23. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol*. 2015; 16(1):57–66. [PubMed: 25524800]
 24. Wetzler M, Dodge RK, Mrozek K, et al. Prospective karyotype analysis in adult acute lymphoblastic leukemia: the cancer and leukemia Group B experience. *Blood*. 1999; 93(11):3983–3993. [PubMed: 10339508]

25. Charrin C, Thomas X, Ffrench M, et al. A report from the LALA-94 and LALA-SA groups on hypodiploidy with 30 to 39 chromosomes and near-triploidy: 2 possible expressions of a sole entity conferring poor prognosis in adult acute lymphoblastic leukemia (ALL). *Blood*. 2004; 104(8):2444–2451. [PubMed: 15039281]
26. Moorman AV, Harrison CJ, Buck GA, et al. Karyotype is an independent prognostic factor in adult acute lymphoblastic leukemia (ALL): analysis of cytogenetic data from patients treated on the Medical Research Council (MRC) UKALLXII/Eastern Cooperative Oncology Group (ECOG) 2993 trial. *Blood*. 2007; 109(8):3189–3197. [PubMed: 17170120]
27. Wood B. 9-color and 10-color flow cytometry in the clinical laboratory. *Arch Pathol Lab Med*. 2006; 130(5):680–690. [PubMed: 16683886]
28. Raff T, Gokbuget N, Luschen S, et al. Molecular relapse in adult standard-risk ALL patients detected by prospective MRD monitoring during and after maintenance treatment: data from the GMALL 06/99 and 07/03 trials. *Blood*. 2007; 109(3):910–915. [PubMed: 17023577]
29. Bruggemann M, Schrauder A, Raff T, et al. Standardized MRD quantification in European ALL trials: proceedings of the Second International Symposium on MRD assessment in Kiel, Germany, 18-20 September 2008. *Leukemia*. 2010; 24(3):521–535. [PubMed: 20033054]
30. Klein, JP.; Moeschberger, ML. *Survival Analysis: Techniques for Censored and Truncated Data*. 2. New York, NY: Springer; 2003.
31. Kantarjian HM, O'Brien S, Smith TL, et al. Results of treatment with hyper-CVAD, a dose-intensive regimen, in adult acute lymphocytic leukemia. *J Clin Oncol*. 2000; 18(3):547–561. [PubMed: 10653870]
32. Larson RA, Dodge RK, Burns CP, et al. A five-drug remission induction regimen with intensive consolidation for adults with acute lymphoblastic leukemia: cancer and leukemia group B study 8811. *Blood*. 1995; 85(8):2025–2037. [PubMed: 7718875]
33. Linker C, Damon L, Ries C, Navarro W. Intensified and shortened cyclical chemotherapy for adult acute lymphoblastic leukemia. *J Clin Oncol*. 2002; 20(10):2464–2471. [PubMed: 12011123]
34. Seftel MD, Neuberg D, Zhang MJ, et al. Superiority of Pediatric Chemotherapy over Allogeneic Hematopoietic Cell Transplantation for Philadelphia Chromosome Negative Adult ALL in First Complete Remission: A Combined Analysis of Dana-Farber ALL Consortium and CIBMTR Cohorts. *ASH Annual Meeting*. 2014; 124 Abstract 319.
35. Roberts KG, Pei D, Campana D, et al. Outcomes of children with BCR-ABL1-like acute lymphoblastic leukemia treated with risk-directed therapy based on the levels of minimal residual disease. *J Clin Oncol*. 2014; 32(27):3012–3020. [PubMed: 25049327]

Figure 1. Flow diagram depicting how patients were designated to each subgroup

Patients were categorized based on whether or not minimal residual disease (MRD) was assessed within 3 months of initiation of treatment, type of treatment (i.e., pediatric vs adult), and whether a minimal residual disease negative (MRD^{Neg}) remission was achieved. Among those who did achieve MRD^{Neg} remission, post-remission therapy consisted either of no hematopoietic cell transplantation (Deferred HCT), myeloablative HCT (MAC), or reduced-intensity HCT (RIC).

Figure 2. Overall survival (OS), event-free survival (EFS), and cumulative incidence of relapse (CIR) of adults with acute lymphoblastic leukemia (ALL) in first minimal residual disease negative (MRD^{Neg}) remission after adult-inspired therapy followed by allogeneic hematopoietic cell transplantation (HCT) with myeloablative conditioning (MAC), reduced-intensity conditioning (RIC), or no transplant (Deferred HCT)

Kaplan-Meier curves depict (A and B) OS, (C and D) EFS, and (E and F) CIR of the (A, C, and E) MAC and RIC groups and (B, D, and F) Deferred HCT group. As discussed in the text, these 3 groups could not accurately be compared together due to the varying times at which MRD^{Neg} was identified. Thus, the MAC and RIC groups are plotted relative to the date of HCT, whereas the Deferred HCT group is relative to the date that MRD^{Neg} was confirmed.

Figure 3. Outcomes after allogeneic hematopoietic cell transplantation (HCT) while in either first or second-or-later minimal residual disease negative remission (MRD^{Neg} CR1 or MRD^{Neg} CR2+, respectively) after adult-inspired initial therapy
 Kaplan-Meier curves depict (A) overall survival, (B) event-free survival, (C) cumulative incidence of relapse, and (D) cumulative incidence of non-relapse mortality, depending on disease status at the time of HCT.

Characteristics of adults with acute lymphoblastic leukemia who achieved a minimal residual disease negative remission with adult-inspired therapy, sub-categorized by subsequent treatment.

Table 1

Patient characteristics	Deferred HCT (N = 39)		MAC (N = 33)		RIC (N = 17)		P+
	N	%	N	%	N	%	
Gender							0.30
Male	18	46%	19	58%	6	35%	
Female	21	54%	14	42%	11	65%	
Age at Diagnosis (years)							0.061
Median	44		42		60		
Range	20-77		20-58		33-67		
At least 35 years old	28	72%	21	64%	16	94%	
Lineage							0.021
B-Cell	27	69%	27	82%	17	100%	
T-Cell	12	31%	6	18%	0	0%	
High WBC?							0.70
Yes	8	20%	6	18%	5	29%	
No	31	79%	27	82%	12	70%	
Cytogenetics							0.002
High Risk	9	23%	17	52%	13	77%	
Other/Normal	27	69%	15	45%	4	23%	
Unknown	3	8%	1	3%	0	0%	
Ph Status							<0.001
Ph+	5	13%	12	36%	13	77%	
Ph-	31	79%	20	61%	4	23%	
Unknown	3	8%	1	3%	0	0%	
Initial Therapy							0.56
HyperCVAD	31	79%	24	73%	15	88%	
Larson	7	18%	6	18%	1	6%	
Linker	1	3%	3	9%	1	6%	

Patient characteristics	Deferred HCT (N = 39)		MAC (N = 33)		RIC (N = 17)		P ⁺
	N	%	N	%	N	%	
Time from Initiation of Treatment to MRD ^{Neg} (months)							0.32
Median	1.4		1.4		2.7		
Range	0.43-9.8		0.43-5.3		0.53-6.0		
1 month or less	7	18%	11	33%	5	29%	
Donor							0.26
Sibling	N/A	N/A	13	39%	5	29%	
Unrelated	N/A	N/A	19	58%	9	53%	
Cord Blood	N/A	N/A	1	3%	1	6%	
Haploidentical	N/A	N/A	0	0%	2	12%	
Stem Cell Product							0.69
PBSC	N/A	N/A	27	82%	15	88%	
Bone Marrow	N/A	N/A	5	15%	1	6%	
Cord Blood	N/A	N/A	1	3%	1	6%	

HCT indicates hematopoietic cell transplantation; MAC, myeloablative conditioning; RIC, reduced-intensity conditioning; WBC, white blood cell count; Ph, Philadelphia chromosome; HyperCVAD, hyperfractionated cyclophosphamide, vincristine, doxorubicin, and dexamethasone alternating with methotrexate and high-dose cytarabine; MRD^{Neg}, minimal residual disease-negative remission; PBSC, peripheral blood stem cells.

[†]P-values are from comparisons made using a Fisher's exact test.

Table II

Results of Cox proportional hazards models comparing outcomes in patients who received myeloablative, reduced-intensity, and no transplantation in first minimal residual disease negative remission following adult-inspired therapy.

All Patients (N = 89)			
Overall Survival (30 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC	0.92	0.29-2.88	0.89
MAC	1.46	0.67-3.18	0.34
Event-Free Survival (47 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC	0.57	0.24-1.38	0.21
MAC	0.58	0.29-1.15	0.12
Relapse (37 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC	0.43	0.17-1.10	0.08
MAC	0.19	0.07-0.51	0.001
Ph- Patients (N = 55) [†]			
Overall Survival (19 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	1.32	0.53-3.30	0.55
Event-Free Survival (29 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	0.53	0.23-1.24	0.23
Relapse (22 events; adjusted for WBC)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	0.10	0.02-0.44	0.003
Ph+ Patients (N = 30)			
Overall Survival (10 events; no adjustments)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	1.08	0.22-5.27	0.92
Event-Free Survival (16 events; no adjustments)			

Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	0.28	0.07-1.19	0.084
Relapse (13 events; no adjustments)			
Group	HR	95% CI	P
Deferred HCT	1	NA	NA
RIC or MAC [†]	0.15	0.03-0.76	0.02

HR indicates hazard ratio; CI, confidence interval; additional abbreviations are explained in Table 1.

[†]4 patients with unknown cytogenetics at diagnosis were excluded from this analysis.

[†]Due to the relatively small numbers of patients, both the RIC and MAC groups were collapsed into a single group for these comparisons.

Table III

Time-to-event comparisons of the no transplant, myeloablative conditioning, and reduced-intensity conditioning groups.

Parameter	Deferred HCT ⁺	MAC ⁺	RIC ⁺
Overall Survival			
1-year	91%	75%	88%
3-year	68%	71%	69%
Event-Free Survival			
1-year	68%	68%	81%
3-year	28%	65%	54%
Cumulative Incidence of Relapse			
1-year	35%	6%	12%
3-year	72%	10%	40%

Abbreviations are explained in Table 1.

⁺ As discussed in the text, for the Deferred HCT group, time is calculated from the point of achieving MRD^{Neg}. For the MAC and RIC groups, time is calculated from the date of HCT.

Characteristics of adults with acute lymphoblastic leukemia who received hematopoietic cell transplantation while in first or second-or-later minimal residual disease negative remission following adult-inspired initial therapy.

Table IV

Patient characteristics	HCT in MRD ^{Neg} CR1 (N = 50)		HCT in MRD ^{Neg} CR2+ (N = 20)		P+
	N	%	N	%	
Gender					0.30
Male	25	50%	13	65%	
Female	25	50%	7	35%	
Age at Diagnosis (years)					0.012
Median	48		30		
Range	20-67		20-51		
35 years	37	74%	8	40%	
Lineage					0.040
B-Cell	44	88%	13	65%	
T-Cell	6	12%	7	35%	
High WBC?					0.54
Yes	11	22%	6	30%	
No	39	78%	14	70%	
Cytogenetics					0.051
High Risk	30	60%	6	30%	
Other/Normal	19	38%	13	65%	
Unknown	1	2%	1	5%	
Ph Status					0.003
Ph+	25	50%	2	10%	
Ph-	24	48%	17	85%	
Unknown	1	2%	1	5%	
Initial Therapy					0.20
HypertCVAD	39	78%	14	70%	
Larson	7	14%	3	15%	
Linker	4	8%	1	5%	

Patient characteristics	HCT in MRD ^{Neg} CR1 (N = 50)		HCT in MRD ^{Neg} CR2+ (N = 20)		P ⁺
	N	%	N	%	
Other	0	0%	2	10%	
MRD negative with initial therapy	50	100%	14	70%	<0.001
HCT Intensity					0.014
MAC	33	66%	19	95%	
RIC	17	34%	1	5%	
Donor					0.045
Sibling	18	36%	8	40%	
Unrelated	28	56%	7	35%	
Cord Blood	2	4%	5	25%	
Haploidentical	2	4%	0	0%	
Stem Cell Product					0.039
PBSC	42	84%	14	70%	
Bone Marrow	6	12%	1	5%	
Cord Blood	2	4%	5	25%	

MRD^{Neg} CR1 indicates first minimal residual disease negative remission; MRD^{Neg} CR2+, second-or-later minimal residual disease negative remission; additional abbreviations are explained in Table 1.

⁺P-values are from comparisons made using a Fisher's exact test.