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

Veronika Bachanova, MD, PhD[1], **David I. Marks, MD, PhD**[2], **Mei-Jie Zhang, PhD**[3], **Hailin Wang, MPH**[3], **Marcos de Lima, MD**[4], **Mahmoud D. Aljurf, MD, MPH**[5], **Martha Arellano, MD**[6], **Andrew S. Artz, MD, MS**[7], **Ulrike Bacher, MD**[8], **Jean-Yves Cahn, MD**[9], **Yi-Bin Chen, MD**[10], **Edward A. Copelan, MD**[11], **William R. Drobyski, MD**[12], **Robert Peter Gale, MD, PhD, Dsc(hon), FACP**[13], **John P Greer, MD**[14], **Vikas Gupta, MD**[15], **Gregory A. Hale, MD**[16], **Partow Kebriaei, MD**[17], **Hillard M. Lazarus, MD**[4], **Ian D. Lewis, MBBS, PhD**[18], **Victor A. Lewis, MD**[19], **Jane L. Liesveld, MD**[20], **Mark R. Litzow, MD**[21], **Alison W. Loren, MD, MS**[22], **Alan M. Miller, MD, PhD**[23], **Maxim Norkin, MD, PhD**[24], **Betul Oran, MD, MS**[17], **Joseph Pidala, MD, MS**[25], **Jacob M. Rowe, MD**[26], **Bipin N. Savani, MD**[14], **Wael Saber, MD, MS**[3], **Ravi Vij, MBBS**[27], **Edmund K. Waller, MD, PhD**[28], **Peter H. Wiernik, MD**[29], and **Daniel J. Weisdorf, MD**[1]

[1]Blood and Marrow Transplant Program, University of Minnesota Medical Center, Minneapolis, MN

[2]Bristol Adult BMT Unit, Bristol Children's Hospital, Bristol, UNITED KINGDOM

[3]Center for International Blood and Marrow Transplant Research (CIBMTR), Medical College of Wisconsin, Milwaukee, WI

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

[5]King Faisal Specialist Hospital and Research Center, Riyadh, SAUDI ARABIA

[6]Winship Cancer Institute, Emory University, Atlanta, GA

[7]University of Chicago Medicine, Chicago, IL

[8]Klinik und Poliklinik fur Stammzelltransplantation, Universitatsklinikum Hamburg-Eppendorf, Hamburg, GERMANY

[9]Department of Hematology, University Hospital, Grenoble, FRANCE

Address for Correspondence: Veronika Bachanova, MD, PhD, Blood and Marrow Transplant Program, University of Minnesota, Mayo Mail Code 480; 420 Delaware Street SE, Minneapolis, MN 55455, bach0173@umn.edu, Phone: 612-624-5620; Fax: 612-625-6919.

[10]Massachusetts General Hospital, Boston, MA

[11]Levine Cancer Institute, Carolinas HealthCare System, Charlotte, NC

[12]Medical College of Wisconsin, Milwaukee, WI

[13]Imperial College, Section of Hematology, Division of Experimental Medicine, Department of Medicine, London, UNITED KINGDOM

[14]Vanderbilt University Medical Center, Nashville, TN

[15]Princess Margaret Hospital, Toronto, ON, CANADA

[16]All Children's Hospital, St. Petersburg, FL

[17]Stem Cell Transplantation and Cellular Therapy, MD Anderson Cancer Center, Houston, TX

[18]Haematology and Bone Marrow Transplant Unit, Royal Adelaide Hospital/SA Pathology, Adelaide, AUSTRALIA

[19]Alberta Children's Hospital, Calgary, AB, CANADA

[20]Strong Memorial Hospital, University of Rochester Medical Center; Rochester, NY

[21]Hematology and Internal Medicine, Mayo Clinic Rochester, Rochester, MN

[22]Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[23]Baylor University Medical Center, Dallas, TX

[24]Shands HealthCare and University of Florida, Gainesville, FL

[25]Blood and Marrow Transplantation, Moffitt Cancer Center, Tampa, FL

[26]Department of Hematology, Rambam Medical Center, Haifa, ISRAEL

[27]Barnes Jewish Hospital, Washington University School of Medicine, St. Louis, MO

[28]Bone Marrow and Stem Cell Transplant Center, Emory University Hospital, Atlanta, GA

[29]Our Lady of Mercy Medical Center, Bronx, NY

Abstract

The efficacy of reduced intensity conditioning (RIC) allogeneic hematopoietic cell transplantation (HCT) for Ph+ acute lymphoblastic leukemia (ALL) is uncertain. We analyzed 197 adults with Ph + ALL in first complete remission; 67 patients receiving RIC were matched with 130 receiving myeloablative conditioning (MAC) for age, donor type, and HCT year. Over 75% received pre-HCT tyrosine kinase inhibitors (TKI), mostly imatinib; 39% (RIC) and 49% (MAC) were MRD^{neg} pre-HCT. At a median 4.5 years follow-up, 1-year transplant-related mortality (TRM) was lower in RIC (13%) than MAC (36%;p=0.001) while the 3-year relapse rate was 49% in RIC and 28% in MAC (p=0.058). Overall survival was similar (RIC 39% [95% CI:27–52] vs. 35% [95% CI:270–44];p=0.62). Patients MRD^{pos} pre-HCT had higher risk of relapse with RIC versus MAC (HR 1.97;p=0.026). However, patients receiving pre-HCT TKI in combination with MRD negativity pre-RIC HCT had superior OS (55%) compared to a similar MRD^{neg} population after MAC (33%; p=0.0042). In multivariate analysis, RIC lowered TRM (HR 0.6; p=0.057), but absence of pre-

HCT TKI (HR 1.88;p=0.018), RIC (HR 1.891;p=0.054) and pre-HCT MRD[pos] (HR 1.6; p=0.070) increased relapse risk. RIC is a valid alternative strategy for Ph+ ALL patients ineligible for MAC and MRD[neg] status is preferred pre-HCT.

Keywords

Acute lymphoblastic leukemia; Philadelphia chromosome; reduced intensity conditioning; allograft; minimal residual disease; tyrosine-kinase inhibitor

INTRODUCTION

Philadelphia chromosome positive (Ph+) acute lymphoblastic leukemia (ALL) is the largest genetically defined subset, affecting about 25% of adults with ALL; particularly those older than 40 years.[1] The poor survival of Ph+ ALL patients treated with chemotherapy alone (10%) has been substantially improved through the use of allogeneic hematopoietic cell transplantation (HCT) in first complete remission (CR1) and more recently, by combining tyrosine kinase inhibitors (TKI) with induction and post-remission chemotherapy.[2–5] The anti-leukemia effect of HCT is through chemotherapy and/or radiation used in the preparative regimen and through an immune-mediated graft-versus-leukemia (GVL) effect.[5–8] Although widespread use of TKIs has changed the landscape of Ph+ ALL management, myeloablative conditioning (MAC) followed by the allogeneic HCT remains the only established curative therapy. Incorporating TKIs into induction chemotherapy has not increased toxicity, but has substantially improved remission rates and facilitated more allotransplants in CR1.[9, 10] Furthermore, several prospective clinical trials testing an imatinib-containing strategy consolidated with a MAC alloHCT showed overall survival (OS) ranging from 40–65%, which is markedly better than historical pre-imatinib controls (OS 20–40%).[2–4, 11–13] However, many patients are not eligible for a conventional myeloablative conditioning regimen due to their age and comorbidities. High transplant-related mortality (TRM) remains a serious problem in older adults which negates the survival benefit gained through protection from relapse by full intensity conditioning and GVL.[14] For these reasons, RIC HCT was developed to allow engraftment and harness the GVL effect while potentially limiting TRM in patients unfit for full intensity conditioning regimens

To date, there are no large-scale data on the efficacy of RIC HCT for Ph+ ALL. Most single institution studies lack detail on ALL subset-specific outcomes.[15–19] The utility of RIC HCT for ALL was recently demonstrated in a CIBMTR study for Ph negative ALL, in which similar rates of TRM, relapse, and survival (43% vs 38%) between RIC and MAC were observed.[20] A European Bone Marrow Transplant (EBMT) Registry study, which included 41 Ph+ patients in a RIC cohort, showed comparable OS between RIC and MAC groups.[21] However, the limited details on minimal residual disease (MRD) and TKI use make the interpretation of these studies problematic. Indeed, the definition of remission in Ph+ ALL now routinely includes tools to assess the depth of remission by cytogenetic testing of interphase cells for t(9;22) (fluorescent in situ hybridization [FISH]) and PCR for detection of chimeric mRNA arising from BCR-ABL1 genomic recombination. FISH assay allows the

sensitivity between 0.5–3%, while real-time PCR and nested PCR allow quantification of MRD to the $1:10^5$-10^6 cell level.[22] Both assays are widely used to monitor response and guide therapeutic choices.[17,23–26] Several studies in adult Ph+ ALL have confirmed that patients with MRD persistence 6–10 weeks after initiating induction therapy have a higher risk of relapse, yet early myeloablative allogeneic donor HCT can sometimes overcome MRD^{pos} and cure a subset of patients.[25, 27] The sensitivity of Ph+ ALL to non-ablative chemotherapy/radiation and to GVL in the setting of RIC HCT is not well established. To address these issues, we performed a multicenter registry-based analysis investigating the outcomes of RIC allogeneic HCT for Ph+ ALL. Using a matched pair design, we examined a cohort of patients with Ph+ALL in CR1 and compared survival after RIC or MAC allogeneic transplantation, as well as the effect of TKI use and pre-HCT MRD status on transplant outcomes.

PATIENTS AND METHODS

Data source

The CIBMTR (Center for International Bone Marrow Transplant Research), a voluntary working group of more than 450 transplantation centers worldwide, collects data on consecutive allogeneic HCTs at a statistical center housed at both the Medical College of Wisconsin (Milwaukee, WI) and the National Marrow Donor Program (Minneapolis, MN). Patients are observed longitudinally with yearly follow-up. Computerized checks for errors and onsite audits of participating centers ensure data quality. The present study was conducted with a waiver of informed consent and in compliance with Health Insurance Portability and Accountability Act regulations as determined by the Institutional Board and the Privacy Officer of the Medical College of Wisconsin.

Patient Selection

We included patients aged 18 and older with Ph+ALL in CR1 who had received HLA allele matched related or matched or mismatched unrelated donor (URD) HCT between 2000 and 2009. Well matched URD were either 8/8 or 6/6 matched at Class 1 as recommended by CIBMTR.[26] Umbilical cord blood donors, mismatched related donor and ex vivo T cell-depleted grafts were excluded. Preparative regimens were classified either as RIC or MAC according to published consensus definitions.[28] The CIBMTR definition of RIC included regimens containing melphalan   150mg/m2 (n=24), busulfan   9mg/kg orally (n=20), total body irradiation <5 Gy (TBI; n=11), fludarabine-TBI combinations (n=17), or fludarabine-based conditioning (n=5). The MAC preparative regimen consisted mostly of TBI (n=108) or busulfan combinations (n=22). RIC patients were matched with MAC patients on 3 factors: age (within 15 years), type of donor (related versus URD), and year of transplant (within 5 years). A supplemental data form was developed to collect: 1) presence of pre-HCT MRD in bone marrow immediately prior to conditioning tested by FISH and/or by PCR for the BCR-ABL (yes/no); and 2) use of TKIs (imatinib, nilotinib or dasatinib) delivered at any time prior to transplantation and the duration of TKI therapy. We also collected data on post-transplant TKI administration, defined as maintenance therapy (excluding treatment given for cytogenetic or morphologic relapse), start date and duration of maintenance. Retrospectively collecting the MRD data from many centers reflects the real

world clinical practice where both BCR/ABL transcript levels and/or FISH analysis are often obtained in patients with morphologic CR. The stringency of MRD determination using each center's testing sensitivity with these approaches could not be addressed in this multicenter analysis. Data on post-transplant MRD monitoring were not collected. The final study population excluded MAC patients not selected by the matching strategy (n=241) and those without supplemental data (n=32). The return rate on supplemental forms requested on 243 cases from 76 centers was 86.4%. Each participating center enrolled an average 2.5 cases (range 1–15 cases).

Definitions, Study Endpoints and Statistical Analysis

The primary outcomes were OS after HCT defined as the time from transplantation to death, disease-free survival (DFS), relapse incidence and TRM. Surviving patients were censored at the time of last contact. Secondary endpoints were grade II-IV acute graft-versus-host disease (aGVHD) and chronic GVHD (cGVHD). Probability of DFS and OS were calculated using the Kaplan-Meier estimator, with the variance estimated by Greenwood's formula. Values for other endpoints were calculated using cumulative incidence curves to accommodate competing risks.[29] We defined the MRD status as MRD^{pos} (Ph+ by FISH positive and/or positive BCR-ABL by PCR) and pre-HCT MRD^{neg} (Ph+ FISH negative and/or negative BCR-ABL by PCR). Use of TKI was defined as pre-HCT TKI (including 41 patients who received TKI both pre and post-HCT) or no TKI at any time-point. The risk factors considered in the stepwise model building procedures were conditioning regimen intensity (main effect), age, gender, pre-HCT MRD positivity, TKI use pre-HCT (yes/no), year of HCT and cGVHD as a time-dependent covariate. The potential interactions between the main effect (conditioning regimen) and MRD, TKI and other significant variables were examined.

RESULTS

Patients Characteristics

Data on 197 eligible patients from 14 different countries and 76 reporting centers were analyzed. Sixty-seven RIC patients were matched for analysis 1:2 (n=63) or 1:1 (n=4) to 130 MAC patients for age, donor type, and year of transplant (Table 1). Median age in the RIC and MAC groups was 54 and 50 years, respectively (p=0.02). WBC count at diagnosis and performance status at time of transplant were similar for both groups. Previous fungal infections were more common in the RIC group (12% vs 3%; p=0.006). RIC recipients had a longer median time from diagnosis to HCT (6 months (interquartile range 4.8–7.4 months) vs MAC: 5 months (interquartile range 4.2–6.8 months; p=0.03), but the time from diagnosis to CR1 was similar (median 42 days (interquartile range 34–82 days) and 52 days (interquartile range 31–111 days; p=0.76) in RIC and MAC groups. Over half of patients in both groups had co-existent morbidities or organ impairment (61% in RIC and 58% in MAC; p=0.12). Significantly more RIC patients had a pre-HCT comorbidity index of 1 as compared to MAC patients (19% vs 8%; p=0.03).[30] Both RIC and MAC groups used peripheral blood grafts more often than bone marrow grafts and had similar use of related donors (39% and 38%) and matched URD (42% for both). GVHD prophylaxis was similar in both groups with cyclosporine or tacrolimus-containing-regimens used most often. RIC

patients more often received anti-thymocyte globulin or campath (37% vs 17%; p=0.03). The remaining variables of donor/recipient sex, donor/recipient CMV status and year of transplant were balanced. Median follow-up of survivors was 49 months (range 3–108 months) for the RIC group and 61 months (range 3–119 months) for the MAC group.

MRD assessment and use of TKI inhibitors

All patients were in CR1 by morphologic criteria. Reflecting the clinical practice, more patients had pre-HCT bone marrow MRD evaluation by FISH (RIC: 89%; MAC: 88%) than PCR (RIC: 64%; MAC: 63%). 185 subjects (94% of all patients; RIC: 97%; MAC: 92%) were investigated by at least one MRD method prior to transplant at median time 25 days (interquartile range: 14–122 days; only 46% reported the MRD test date). Similar proportions of RIC and MAC recipients were FISH[pos] (34% vs 38%), PCR BCR/ABL[pos] (50% vs 35%) and positive by either or both methods (MRD[pos] 58% and 47%; p=0.79; Table 1).

Before 2005, 60% received TKI pre-transplant compared to nearly 90% after 2005 (p<0.01). All but 2 patients received imatinib pre-HCT (the pre-HCT TKI group); including who 2 received dasatinib pre-HCT. The median duration of TKI pre-HCT was 7 months (RIC) and 6 months (MAC). Among 153 patients given TKI pre-HCT, 41% became MRD[neg] pre-HCT. Among 44 patients not receiving TKI, 48% were MRD[neg]. The rate of MRD negativity was not better in those receiving prolonged pre-HCT TKI (>6 months 38% vs <6 months 42%; p=0.44).

Only 43 (<25%) patients (RIC n=21; MAC n=22) received TKI post-transplant for maintenance. Data on the drug, dose, and treatment duration were not available. The majority of patients (90% in RIC and 77% in MAC) who received TKI post-transplant were MRD[pos] pre-HCT. The median time to TKI administration after RIC HCT was 1.5 months (interquartile range: 0.9 –3.5 months), about 1 month earlier than MAC HCT (2.9 months [interquartile range 1.7–5.5 months]; p=0.095). Forty-one patients (20%) were not treated with TKI agents at any time.

DFS and OS

At 3 years, DFS and OS for the RIC group were 26% (95% CI 16–37%) and 39% (95% CI 27–52%), respectively and were similar to the MAC group (28% [95%CI 20–36%] and 35% [95%CI 27–44%]; Table 2). In univariate analysis, pre-HCT MRD status did not impact survival in either group (Figure 1B). Sex, peripheral WBC at diagnosis and year of HCT did not significantly affect OS in univariate analysis (male gender HR: 1.17 (95%CI 0.8–1.6); WBC>100×10^9/L: HR 0.6 [95%CI 0.32–1.1], 2005–2009 HR: 1.05 [95%CI 0.7–1.5]. Within the RIC group, both pre-HCT TKI and concomitant MRD[neg] status yielded the best 3-year OS (55% [95%CI 31–77%]), which compared favorably to the same patients (MRD[neg] with pre-HCT TKI) in the MAC group (33% ([95% CI 20–48%]); p= 0.0042).

In multivariate analysis, RIC did not significantly influence OS (HR 0.87; p=0.48) or DFS (HR 1.1; p=0.58; Table 3). Age above 40 years was associated with significantly worse survival (HR 1.92), but pre-HCT MRD status, pre-HCT TKI use and the development of cGVHD did not significantly alter OS or DFS (Table 3).

TRM and Causes of Death

The cumulative incidence of TRM at day 100 was 10% in the RIC group (95% CI 4–19%) and 19% in the MAC group (95%CI 13–26%; p=0.11), while at 1 year it was almost 3-fold lower in the RIC than in the MAC group (13% vs 36%; p<0.001; Figure 1C). In adjusted multivariate analysis, RIC was associated with reduced TRM risk (HR 0.60; p=0.059). Age over 40 years increased the risk of TRM 3-fold and cGVHD increased TRM risk 1.7-fold (Table 3). The most common cause of death in the RIC group was relapse (n=13) followed by infection (n=10), organ failure (n=6), and GVHD (n=4). MAC patients died most often of GVHD (n=22), relapse (n=16), and infection (n=12). Death attributed to GVHD was more common after MAC compared to RIC HCT (p=0.1).

Relapse

The incidence of relapse at 3 years was higher in the RIC group (49%) than in the MAC group (28%) although not statistically significant (p=0.058; Table 2). Given that pre-HCT MRD and use of TKI could potentially modify relapse risk, we examined relapse risks in specified subgroups. The cumulative incidence of relapse at 3 years in pre-HCT MRD^{pos} patients was significantly higher after RIC 61% (95%CI 45–76%]) than MAC HCT (35% [95% CI 24–48%]; HR 1.97 [1.09–3.57; p=0.026]; Figure 1A). However, pre-HCT MRD^{neg} patients had similar relapse risks after RIC or MAC transplants (31% [95% 15–50%]) vs 21% [11–32%]); p=0.15). Low relapse rate was also observed in subset of patients who were pre-HCT BCR/ABL^{neg} (RIC 16% [95%CI 7–28]; MAC 25% [9–46%]; p=0.36).

In the RIC group, pre-HCT TKI therapy was associated with 2-fold reduction in 3- year relapse incidence (38%[95% CI 25–52%]) as compared to no pre-HCT TKI (81% [95%CI 59–96%]; p=0.0039). In contrast, in the MAC group no protection from relapse by pre-HCT TKI was observed (26% [95%CI, 18%–35%] vs 33% [95%CI 17–52%]; p=0.51). Remarkably low rates of relapse were observed in patients who received pre-HCT TKI who were also pre-HCT MRD^{neg} (RIC 17% [95%CI 4–37%] and MAC HCT 20% [95%CI, 10–33%]). For these patients, the conditioning regimen intensity did not influence relapse risk. The 3-yr relapse was not impacted by TKI post-transplant maintenance neither in the RIC cohort (TKI maintenance 59% vs. no TKI 45%; p=0.63) nor in the MAC cohort (TKI maintenance 27% vs no TKI 28%; p=0.26), although only 43 patients were treated with TKI post-transplant. The median time from HCT to relapse was similar at 11 months in the RIC group (range 1–103 months) and 9 months in the MAC group (range 1–119 months; p= 0.60).

In adjusted multivariate analysis, RIC was associated with increased risk of relapse (HR 1.84; p=0.011). While age (>40 years) and cGVHD did not influence relapse risk, no TKI use pre-HCT (HR 1.88; p=0.018) was independently associated with an increased risk of relapse. Pre-HCT MRD^{pos} (HR 1.6, [95%CI 0.96–2.67]) was associated with increased relapse risk, but did not reach statistical significance (Table 3).

Donor lymphocyte infusions and second transplant

Fourteen patients received donor lymphocyte infusion (DLI) post-transplant (RIC 3; MAC 11). Six DLI infusions were administered for relapsed ALL and all were in the MAC cohort.

None of the 6 patients survive. Three of 8 patients who received DLI for non-relapse indications are alive (two in RIC and one in MAC cohort). Seventeen other patients underwent second HCT for relapsed ALL (RIC cohort 6; MAC cohort 11) and three (17%) survive (2 in RIC and 1 in the initial MAC cohort) after their 2nd HCT.

GVHD

The cumulative incidence of Grade II-IV aGVHD at day 100 was lower in the RIC (30% [95%CI 20–42%]) than the MAC group (47% [95%CI 39–56%]; p=0.014). The incidence of cGVHD at 1 year was similar (RIC 46% [95% 34–58%] vs. MAC 41% [95%CI 32–50%]; p=0.38). Given the recent use of TKIs for treatment of cGVHD, we analyzed the relationship between GVHD and TKI administration after HCT. The median time from HCT to aGVHD diagnosis was 0.9 month (range 0.2–2.7 months), while the median time to start TKI therapy post-transplant was later: 2.3 months (range 0.5–36 months). More importantly, the time from HCT to cGVHD onset was similar in the subgroup treated with TKI (4.4 months) versus no TKI therapy (5.8 months). Additionally, TKI administration post HCT did not reduce the incidence of cGVHD as the proportion of patients with cGVHD was similar with or without post-HCT TKI (63% vs 45%; p= 0.87). In multivariate analysis, pre-HCT MRD and TKI use did not impact risks of acute or chronic GVHD. After adjusting for age, MRD and TKI use, the risk of aGVHD was significantly lower in the RIC group (HR 0.54; p=0.014; Table 3), while the risk of cGVHD was not altered by conditioning regimen intensity.

Discussion

To examine the role of conditioning regimen intensity, MRD and TKI influences on HCT for ALL, we conducted a multicenter retrospective matched-pair analysis of 197 Ph+ ALL patients undergoing RIC and MAC allogeneic HCT in CR1. The strength and clinical applicability of this study is enhanced by the incorporation of data on pre-HCT MRD status and administration of TKI pre-HCT-- two critical outcome-modifying variables. In addition, given the matched pair study design, the median age of 52 years closely reflects the HCT population with Ph+ ALL.

The main finding is that DFS and OS in Ph+ ALL were similar after RIC and MAC allogeneic HCT, confirming the curative potential of allogeneic HCT after a reduced intensity preparative regimen. The relatively mature follow-up of 4 years suggests that long-term survival can be achieved for about 40% of older patients with Ph+ ALL after RIC HCT. Hence, RIC extends the benefit of allotransplant to patients above age 50 and to those who are otherwise ineligible for conventional MAC HCT. While there is still considerable room for improvement, these results are encouraging given the disappointing long-term outcomes observed without HCT. In some studies, patients ineligible for HCT have been treated with TKI-based maintenance therapy.[3, 4, 31, 32] Although early results with short follow-up were promising, late relapses still occurred after a median duration of remission of 20–25 months and this approach currently cannot be considered curative. Most relapses were associated with a highly resistant phenotype and BCR-ABL gene mutations including

T315I.[33, 34] As a result, the value of RIC HCT compared to chemotherapy plus TKI for older patients with Ph+ ALL remains a key issue for future prospective trials.

RIC HCT conferred the most significant benefit to the patients who were MRD[neg] prior to allograft and had received TKI pre-HCT. Indeed, the 2-fold increase in relapse in patients with pre-HCT MRD[pos] evident only in the RIC group suggests that a less intense regimen may not overcome the presence of residual detectable leukemia and that caution is needed when RIC is considered for MRD[pos] patients. Notably, higher use of ATG in RIC group may contribute to higher relapse risk.[35] Nevertheless, the favorable outcomes in MRD[neg] patients suggest that achieving a MRD negative state prior to HCT is vitally important and highlight the need to use effective therapy or perhaps second/third generation TKI pre-HCT for those MRD[pos] patients in whom RIC is planned.[38] In our study, both pre-HCT TKI and MRD[neg] status in RIC patients best protected patients from relapse (only 17% relapsed) and were associated with superior OS of 55%. Use of TKI pre-HCT could lead to deeper MRD negativity; however off-target immunomodulatory antileukemia effects of TKI have been also reported. Interestingly, recent clinical studies suggested development of BCR-ABL-specific cytotoxic T cells in the bone marrow of patients with Ph+ ALL during long-term imatinib treatment.[36] In addition to TKI, other targeted therapeutic interventions such as blinatumomab and cellular infusions could also be of benefit if used prior to RIC HCT or peritransplant.[36–40]

Importantly, we showed that reducing the intensity of the preparative regimen can substantially lower risks of acute GVHD and TRM. This finding is particularly important because higher risks of TRM limit the utility of HCT, particularly for older individuals in whom Ph+ ALL is often diagnosed.[14] The observed low TRM (13% at 1 year) is striking, even acknowledging the inherent selection bias associated with RIC patients, who are usually at a greater risk of transplant-related toxicity.

Because of the retrospective registry study design, we were not able to quantify the depth of MRD and its influence on survival. Both assays have limitations and while PCR is highly sensitive, false negative results can be seen due to exquisite susceptibility of RNA to degradation.[22] Variations in transcript levels detectable by PCR complemented by assessment using FISH temper the implications of these data and highlight the need for prospective validation using standardized BCR/ABL testing. Nevertheless, Ph+ ALL remains an important ALL subset for which RIC HCT is being tested and until prospective trial results become available, our analysis provides real life, clinically relevant insights on allograft approaches for patients with Ph+ALL in morphologic remission. Current evidence suggests that MRD[pos] status after induction/consolidation chemotherapy predicts for an increased risk of relapse and worse survival. In a prospective study by Bassan et al. on 236 patients; 48% remained MRD[pos] after induction/consolidation and 36 patients (66%) underwent HCT rescuing a proportion of MRD[pos] by MAC HCT.[41] Our data also suggest that MAC allotransplantation can reduce the adverse relapse risk conferred by a pre-HCT MRD[pos] status. Other studies reported evidence that MRD[pos] patients treated with allogeneic HCT can have successful outcomes,[24–,26] although post-transplant persistence of MRD[pos] most often predicts imminent relapse and poor DFS. A recent GRALL report showed improved OS after imatinib-based chemotherapy followed by MAC HCT (50%)

compared to no allo-HCT (33%). Although MRD[pos] predicted higher risk of relapse, it did not influence OS.[4]

The emerging future question of great importance is the value serial monitoring of BCR/ABL post-transplant and screening for BCR/ABL mutations. Impact of post-HCT TKI on relapse in this study has to be interpreted with caution because 70–80% of patients did not receive TKI post-HCT in maintenance. This might reflect the earlier era of study or poor tolerance of TKI post-transplant related to myelosuppression or other adverse effects as reported.[11,42] A recent German prospective trial randomized Ph+ ALL patients after MAC HCT to receive either maintenance imatinib or pre-emptive therapy with imatinib for molecular relapse. They concluded that post-transplant imatinib was often delayed or interrupted, but no difference in survival was observed with either approach. The study reported excellent OS of 70% in both groups; however, only those patients who were alive at day 60 were included in the analysis.[42]

Other strategies of post-HCT manipulations such as DLI and second transplant are often available. Though rarely used in our cohort, these efforts did not significantly alter the outcome.

Our results provide directly applicable clinical data for clinicians and supports prospective application of RIC for Ph+ ALL patients who are ineligible for MAC such as the current prospective UKALL 14 clinical trial which offers RIC HCT to Ph+ ALL patients older than 40. Our results suggest that achieving MRD[neg] status may lead to low relapse and prolonged survival from either MAC or RIC HCT and that MRD status and fitness rather than a predefined age cut-off may better guide decisions about conditioning intensity prior to allogeneic HCT. The use of TKI post- transplant requires further study before it can be considered standard of care.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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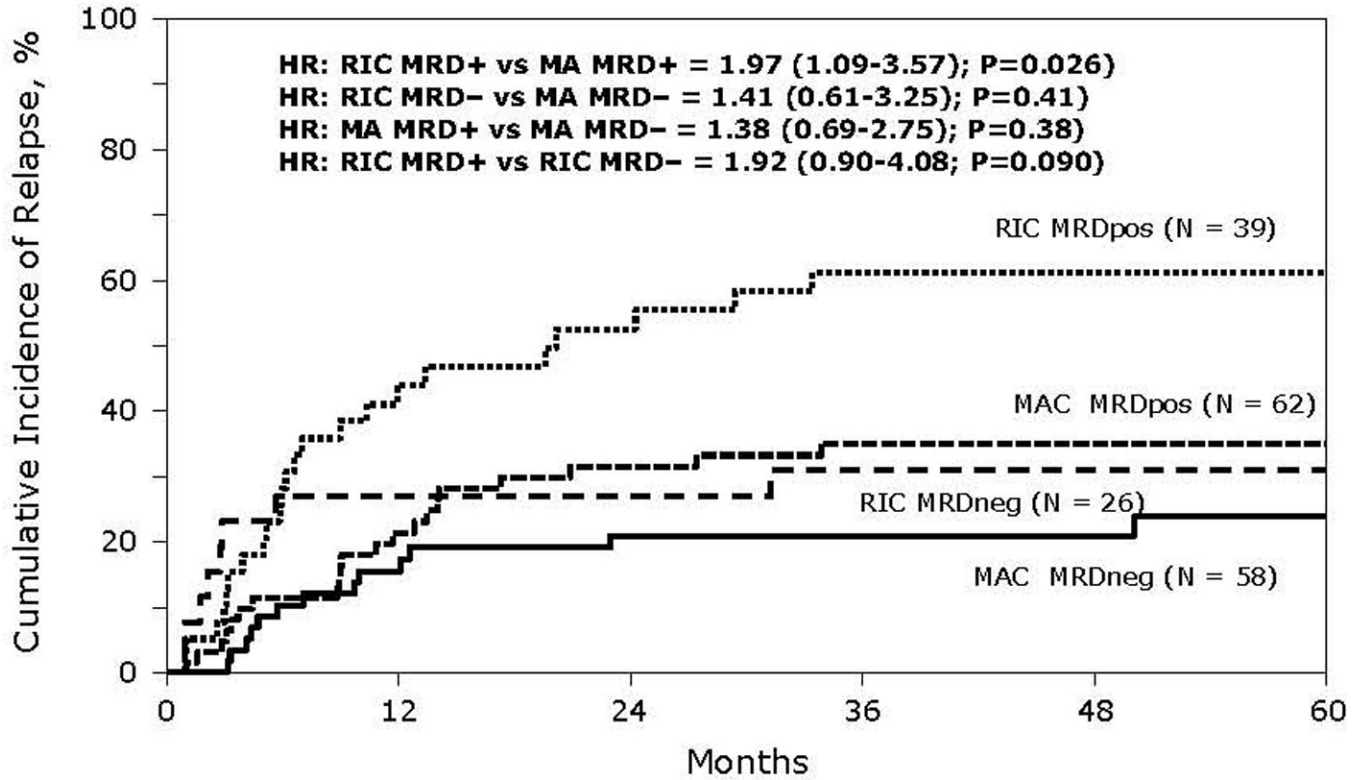
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A.

Cumulative Incidence of Relapse by Conditioning Group with MRD

HR: RIC MRD+ vs MA MRD+ = 1.97 (1.09-3.57); P=0.026)
HR: RIC MRD− vs MA MRD− = 1.41 (0.61-3.25); P=0.41)
HR: MA MRD+ vs MA MRD− = 1.38 (0.69-2.75); P=0.38)
HR: RIC MRD+ vs RIC MRD− = 1.92 (0.90-4.08; P=0.090)

RIC MRDpos (N = 39)

MAC MRDpos (N = 62)

RIC MRDneg (N = 26)

MAC MRDneg (N = 58)

Cumulative Incidence of Relapse, %

Months

B.

Probability of Overall Survival by Conditioning Group with MRD

HR: RIC MRD+ vs MAC MRD+ =0.89 (0.53-1.48; P=0.64)
HR: RIC MRD- vs MAC MRD- =0.72 (0.40-1.29; P=0.28)
HR: MAC MRD+ vs MAC MRD- =0.86 (0.56-1.33; P=0.50)
HR: RIC MRD+ vs RIC MRD- =1.05 (0.56-2.00; P=0.87)

RIC MRDneg (N = 26)
RIC MRDpos (N = 39)
MAC MRDpos (N = 62)
MAC MRDneg (N = 58)

C.

Cumulative Incidence of Treatment-related Mortality

HR: RIC vs MAC=0.57 (0.33-0.98; P=0.041)

MAC (N = 130)

RIC (N = 67)
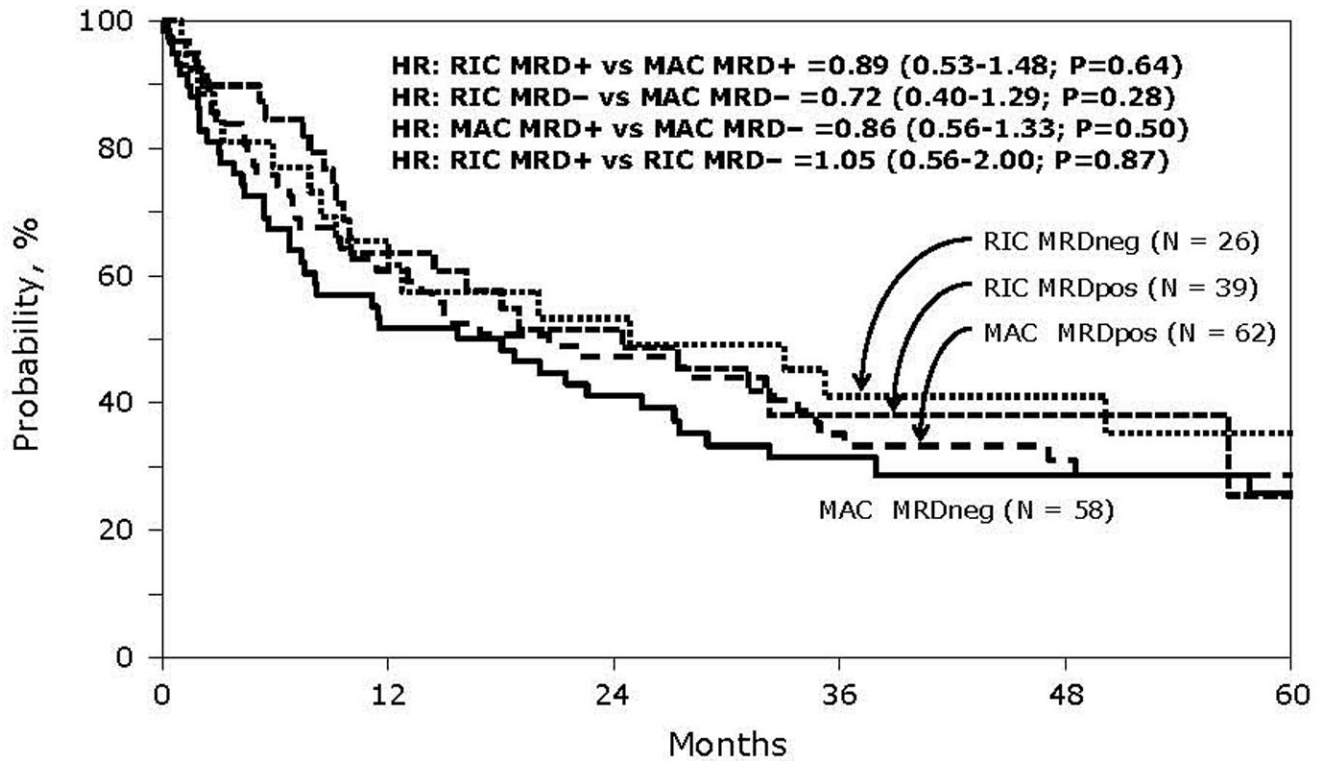
Figure 1.

(A) Kaplan-Meier estimate of overall survival using reduced intensity or myeloablative conditioning HCT for Ph+ ALL by MRD status

(B) Cumulative incidence of relapse by pre HCT MRD and conditioning intensity

(C) Cumulative incidence of treatment related mortality

Table 1

Characteristics of adults with Ph+ ALL who received reduced intensity conditioning (RIC) allogeneic donor HCT in CR1 between 2000–2009 and a matched cohort receiving myeloablative (MAC) allogeneic HCT

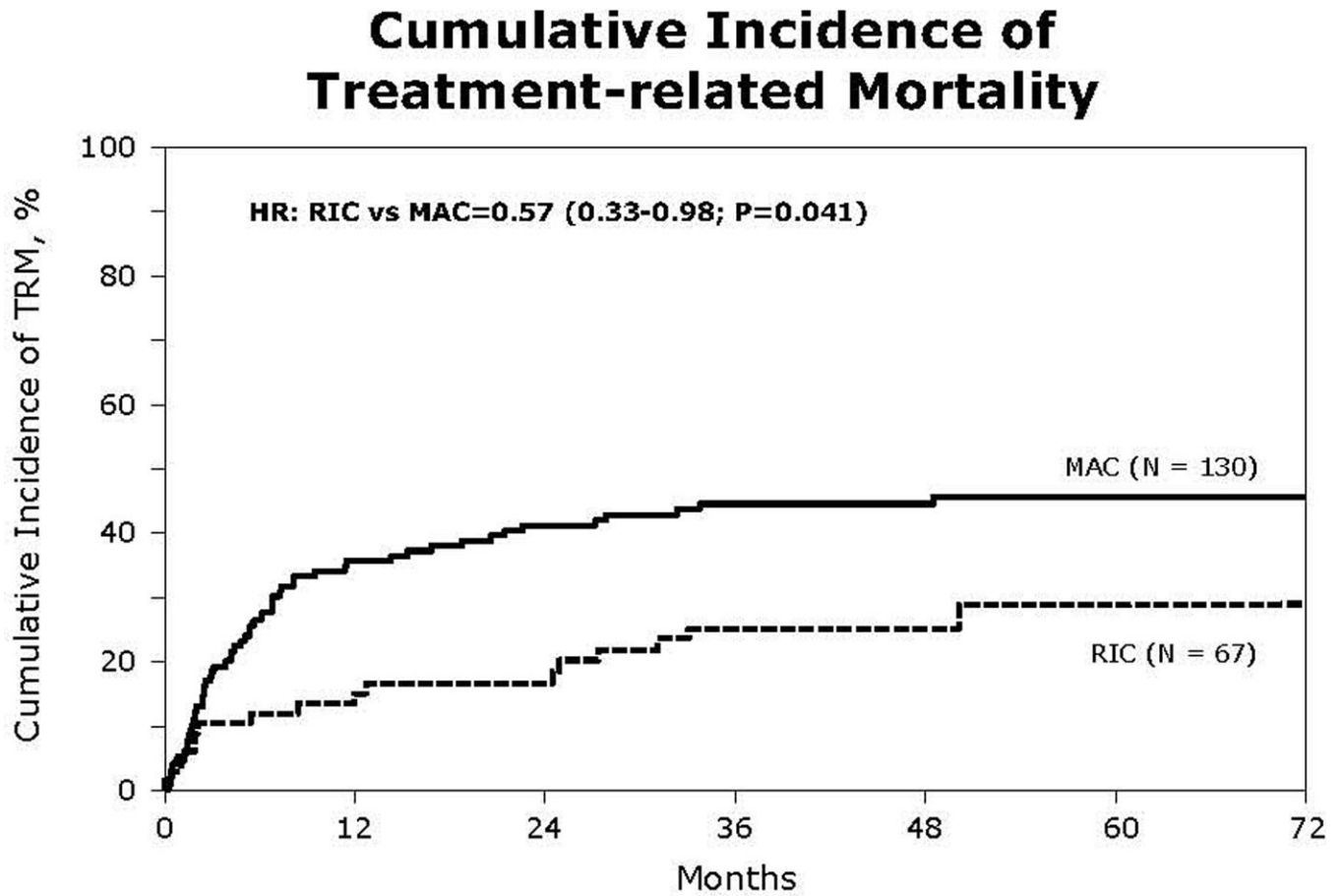| Variable	RIC	MAC	P-value
Number of patients	67	130	
Number of centers	30	66	
Age, median (range)	54 (19–69)	50 (19–66)	0.02
Sex			0.94
Male	37 (55)	71 (55)	
Female	30 (45)	59 (45)	
Karnofsky score			0.36
< 80%	8 (12)	8 (6)	
80 – 100%	54 (81)	113 (87)	
Missing	5 (7)	9 (7)	
HCT Comorbidity Index			0.03
0	54 (81)	119 (92)	
1	13 (19)	11 (8)	
Fungal infection prior to HCT			0.006
No	57 (85)	126 (97)	
Yes	8 (12)	4 (3)	
Missing	2 (3)	0	
WBC at diagnosis, ×10^9/L			0.23
< 30	41 (61)	70 (54)	
30 – 100	14 (21)	23 (18)	
> 100	5 (7)	24 (18)	
Missing	7 (10)	13 (10)	
Cytogenetic abnormalities			0.34
t(9:22) only	32 (48)	48 (37)	
t(9:22) and other	25 (37)	58 (45)	
Other	4 (6)	5 (4)	
Missing	6 (9)	19 (15)	
Time from diagnosis to 1st complete remission			0.76
Median (interquartile range) in days	42 (34–82)	52 (31–111)	
Missing	1 (1)	7 (5)	
Time from diagnosis to transplant			0.02
5 months	20 (30)	64 (49)	
> 5 months	46 (69)	66 (51)	
Missing	1 (1)	0	
Minimal residual disease pre-HCT			
FISH tested	59 (88)	113 (87)	0.75
FISH neg/tested for MRD	36/59 (54)	63/113 (48)	
FISH pos/tested for MRD	23/59 (34)	50/113 (38)	

Variable	RIC	MAC	P-value
FISH not performed or unknown	8 (12)	17 (13)	
BCR/ABL PCR tested	42 (63)	82 (63)	0.73
PCR neg/tested for MRD	21/42 (50)	46/82 (35)	
PCR pos/tested for MRD	21/42 (50)	36/82 (28)	
PCR not performed or unknown	24 (36)	48 (37)	
MRD^{neg}**	26 (39)	58 (49)	0.79
MRD^{pos}*	39 (58)	62 (47)	
TKI use prior to HCT			0.71
No	16 (24)	28 (22)	
Yes	51 (76)	102 (78)	
Duration of TKI pre HCT, months			0.41
Median (range)	7 (1–12)	6 (1–54)	
<6 month	28 (42)	66 (51)	
6 month	15 (22)	18 (14)	
TKI not given or unknown	24 (36)	48 (36)	
Conditioning regimen			N/A
MAC			
TBI>500 cGy single dose or > 800cGy	0	108 (83)	
Busulfan > 9 mg/kg + other	0	22 (17)	
RIC (includes non-myeloablative)			
Melphalan 150 mg/m^2	24 (36)	0	
Busulfan 9 mg/kg	20 (30)	0	
TBI 200 cGy dose$^{#}$	18 (26)	0	
Fludarabine + other	5 (7)	0	
Total body irradiation			N/A
No	45 (67)	22 (17)	
Yes	21 (31)	108 (83)	
Missing	1 (1)	0	
Type of donor			0.10
HLA - identical sibling	26 (39)	50 (38)	
Well - matched URD	28 (42)	54 (42)	
Partially – matched/ mismatched URD	5 (7)	21 (16)	
URD (matching unknown)	8 (12)	5 (4)	
Donor –Recipient sex match			0.79
Male-Male	22 (33)	47 (36)	
Male-Female	18 (27)	40 (31)	
Female-Male	15 (22)	24 (18)	
Female-Female	12 (18)	18 (14)	
Missing	0	1 (<1)	
Donor-Recipient CMV match			0.55
Donor positive/Recipient positive	27 (40)	39 (30)	

Variable	RIC	MAC	P-value
Donor positive/Recipient negative	9 (13)	15 (12)	
Donor negative/Recipient positive	14 (21)	35 (27)	
Donor negative/Recipient negative	15 (22)	38 (29)	
Missing	2 (3)	3 (2)	
Graft type			0.12
Bone marrow	15 (22)	43 (33)	
Peripheral blood	52 (78)	87 (67)	
Year of transplant			0.53
2001–2004	40 (59)	70 (54)	
2005–2009	27 (41)	60 (46)	
GVHD prophylaxis			0.36
Tacrolimus ± other	61 (46)	72 (58)	
Cyclosporine ± other	30 (45)	47 (36)	
ATG/alemtuzumab	25 (37)	23 (17)	0.032
Other	6 (8)	9 (7)	
Median follow-up of survivors: months (range)	49 (3–108)	61 (3–119)	
Post-transplant therapy			
Any TKI given as maintenance post-HCT			0.02
No	46 (69)	108 (83)	
Yes	21 (31)	22 (17)	
Duration of TKI given for maintenance post-HCT			0.05
< 3 months	7 (10)	4 (3)	
3–12 months	9 (13)	9 (7)	
12 months	4 (6)	9 (7)	

[*]
Includes both FISH and/or BCR/ABL PCR positive,

[**]
Includes FISH negative and BCR/ABL PCR negative or missing,

[#]
one patient received TBI <500 cGy single dose

Abbreviations: ALL acute lymphoblastic leukemia, RIC reduced intensity conditioning, MAC myeloablative conditioning, HCT hematopoietic cell transplantation, MRD minimal residual disease, TKI tyrosine kinase inhibitor, CMV cytomegalovirus, TBI total body irradiation, GVHD graft versus host disease,

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Table 2

Outcomes after HCT: Univariate analysis

	RIC		MAC	P-value
	N Eval	Prob (95% CI)	N Eval	Prob (95% CI)	
Relapse	67		130		
3-year		49 (37–61)%		28 (20–36)%	0.058
Treatment related mortality	67		130		
1-year		13 (6–23)%		36 (28–44)%	<0.001
Disease free survival	67		130		
3-year		26 (16–37)%		28 (20–36)%	0.75
Overall survival	67		130		
3-year		39 (27–52)%		35 (27–44)%	0.62
Acute GVHD, grade II – IV	66		130		
100-day		30 (20–42)%		47 (39–56)%	0.014
Chronic GVHD at 3 years	66	60 (47–72)%	128	47 (38–56)%	0.17

Table 3

Multivariate analysis of acute GVHD, chronic GVHD, treatment related mortality, relapse, disease free survival and overall survival

Outcomes	N	HR (95% CI)	P-value
Acute GVHD:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	0.54 (0.33–0.88)	0.014
Chronic GVHD:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	1.23 (0.81–1.86)	0.34
Other factors:			
Pre HCT TKI			
Yes	153	1.00	
No	44	0.88 (0.53–1.45)	0.62
Treatment related mortality:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	0.60 (0.35–1.02)	0.059
Other factors:			
Age			
40 years	42	1.00	
> 40	155	3.24 (1.45–7.24)	0.0042
Minimal residual disease*			
MRD[neg]	84	1.00	$P_{overall}$=0.33
MRD[pos]	101	0.72 (0.45–1.16)	0.18
MRD unknown	12	0.65 (0.25–1.69)	0.37
Pre-HCT TKI			
Yes	153	1.00	
No	44	0.66 (0.38–1.15)	0.14
Chronic GVHD (time dependent)			
No	101	1.00	
Yes	96	1.74 (0.97–3.11)	0.064
Relapse:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	1.84 (1.15–2.94)	0.011
Other factors:			
Age			

Outcomes	N	HR (95% CI)	P-value
40 years	42	1.00	
> 40	155	1.02 (0.61–1.68)	0.95
Minimal residual disease*			
MRD^{neg}	84	1.00	P$_{overall}$=0.13
MRD^{pos}	101	1.60 (0.96–2.67)	0.070
MRD unknown	12	0.77 (0.22–2.78)	0.69
Pre-HCT TKI			
Yes	153	1.00	
No	44	1.88 (1.11–3.17)	0.018
Chronic GVHD (time dependent)			
No	101	1.00	
Yes	96	0.72 (0.40–1.31)	0.28
Disease free survival:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	1.08 (0.76–1.51)	0.68
Other factors:			
Age			
40 years	42	1.00	
> 40	155	1.68 (1.11–2.56)	0.015
Minimal residual disease*			
MRD^{neg}	84	1.00	P$_{overall}$=0.56
MRD^{pos}	101	1.06 (0.75–1.48)	0.75
MRD unknown	12	0.67 (0.29–1.54)	0.35
Pre-HCT TKI			
Yes	153	1.00	
No	44	1.08 (0.75–1.54)	0.69
Chronic GVHD (time dependent)			
No	101	1.00	
Yes	96	1.02 (0.68–1.54)	0.92
Overall survival:			
Main effect:			
Myeloablative conditioning	130	1.00	
Reduced intensity conditioning	67	0.85 (0.59–1.24)	0.41
Other factors:			
Age			
40 years	42	1.00	
> 40	155	1.90 (1.19–3.04)	0.0070
Minimal residual disease*			

Outcomes	N	HR (95% CI)	P-value
MRD^{neg}	84	1.00	P$_{overall}$=0.66
MRD^{pos}	101	0.94 (0.65–1.34)	0.71
MRD unknown	12	0.67 (0.28–1.62)	0.37
Pre-HCT TKI			
Yes	153	1.00	
No	44	1.01 (0.69–1.48)	0.96
Chronic GVHD (time dependent)			
No	101	1.00	
Yes	96	1.15 (0.77–1.74)	0.49