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The Role of Donor Lymphocyte Infusion (DLI) in Post Hematopoietic Cell Transplant (HCT) Relapse for Chronic Myeloid Leukemia (CML) in the Tyrosine Kinase Inhibitor (TKI) Era

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Abstract

Treatment for relapse of chronic myeloid leukemia (CML) following hematopoietic cell transplantation (HCT) includes tyrosine kinase inhibitors (TKI) with or without donor lymphocyte infusions (DLI), however the most effective treatment strategy is unknown. This study was performed through the Center for International Blood and Marrow Transplant Research (CIBMTR) database. We retrospectively reviewed all patients reported to the CIBMTR registry from 2002–2014 who underwent HCT for CML and were alive 30 days post relapse. A total of 215 HCT recipients relapsed and were analyzed in the following groups 1) TKI alone n=128, 2) TKI with DLI n=48, and 3) DLI without TKI n=39. In multivariate analysis, disease status prior to HCT had a significant effect on overall survival (OS). Patients that received a DLI alone compared to a TKI with DLI had inferior survival HR 2.28 (95% CI 1.23–4.24; p = 0.009). Those who received TKI alone had similar survival compared to those who received TKI with DLI (p=0.81). These data supports that despite use of TKI pre-transplantation, TKI salvage therapy continues to provide significant survival following relapse in patients with CML following HCT. These data does not suggest that adding a DLI to TKI adds an improvement in OS.

Introduction

The optimal approach to patients with chronic myeloid leukemia (CML) that relapse following allogeneic hematopoietic cell transplantation (HCT) in the tyrosine kinase inhibitors (TKIs) era is unknown. Imatinib was introduced in 2001 being followed by the

introduction of second generation TKIs such as dasatinib or nilotinib, in subsequent years.[1–2] In later years, the spectrum of TKIs has further broadened, given the introduction of bosutinib and ponatinib.[3–4] Nevertheless, allogeneic HCT remains an important rescue strategy for some CML patients at adverse risk. Currently HCT is indicated in patients with advanced phase CML at disease presentation or disease progression to blast phase.[5] Also HCT is indicated in patients with a lack of response from multiple TKIs or in patients who cannot tolerate TKIs.[5–6] Allogeneic HCT also may be discussed in the case of ABL1 mutations conferring a high resistance level such as T315i mutations.[7] In contrast, prior to the TKI era, patients were evaluated for HCT early during their disease course, especially in younger patients with low comorbidity.

Strategies to treat relapse following HCT have historically relied on the use of donor lymphocyte infusions (DLIs). The graft-versus-leukemia effect is well-described in CML and DLIs have been shown to induce durable remissions in CML.[8–9] Since the approval of imatinib, the tyrosine kinase inhibitors have been used as maintenance therapy following HCT and at disease relapse.[5,9–16] Several small studies have demonstrated benefit in combining DLIs with TKIs.[17–19] In this analysis, we examine outcomes following relapse after HCT in patients that received TKI in combination with DLI (*Combination arm*), TKI without DLI (*Primary TKI*) and DLI without TKI (*Primary DLI*).

Materials and Methods

Data Source

This is a registry-based retrospective study using the Center for International Blood & Marrow Transplant Research (CIBMTR) database. This includes a collaboration of more than 420 transplant centers in the United States and worldwide. Registration and research data are collected pre-transplantation, at 100 days and 6 months post-transplantation, and annually thereafter until death or last follow-up.

Patients

This was a multi-institutional, retrospective study using data from patients with CML who had received TKI, and subsequently underwent HCT from an allogeneic donor, and relapsed following transplantation. The median time to DLI post HCT relapse was 4 weeks, therefore, one-month post HCT relapse was used as a landmark to avoid selection bias against DLI due to early death post HCT relapse. Data were retrieved from CIBMTR from 134 centers during the years of 2002–2014. Treatment at relapse was determined and grouped into three arms 1) TKI in combination with DLI (*Combination arm*), 2) TKI without DLI (*Primary TKI*) and 3) DLI without TKI (*Primary DLI*). Further patient related variables included age, gender, and Karnofsky Performance Status (KPS). Disease related variables included disease status prior to HCT, time from diagnosis to HCT, time from HCT to relapse, time from diagnosis to relapse. Transplant related variables assessed included donor type, HLA match, year of transplant, graft source, cytomegalovirus (CMV) status, conditioning regimen, graft-versus-host disease (GVHD) prophylaxis, and presence or absence of planned TKI maintenance. Patients were also assessed for presence of GVHD (acute II-IV/chronic) prior

to the landmark analysis. Patients were excluded if they did not receive a TKI prior to HCT. Umbilical cord blood were excluded due to patients not able to undergo DLI.

Definitions

HLA 'well matched' is defined as no identified HLA mismatch and informative data at 4 loci or allele matching at HLA-A, -B and –DRB1; 'partially matched' is defined as single-locus mismatch and/or missing HLA data.[20] Myeloablative conditioning (MAC) is defined as irreversible cytopenia and stem cell support is mandatory.[21] Nonmyeloablative (NMA) is defined as causing minimal cytopenia and can be given also without stem cell support. [21] Reduced-intensity conditioning (RIC) is defined as not fitting criteria for either MAC or NMA. [21] Criteria used to identify acute GVHD and chronic GVHD are as defined by Glucksberg et al. and Shulman et al.[22–23] Variables were reported and collected from the CIBMTR forms and defined in the CIBMTR manual (e.g. relapse).

Statistical Analysis

Descriptive statistics tables of patients including demographics, disease-related factors, transplant-related factors and cause of death were prepared. Medians and ranges were listed for continuous variables. The total numbers of patients and the percentages of each subgroup were calculated for categorical variables. Baseline characteristics of patients were compared between three relapse treatment groups, "TKI + DLI" vs. "TKI without DLI" vs. "DLI without TKI", using chi-square test for categorical variables and the Kruskal-Wallis test for continuous variables.

The Cox proportional hazards model was used for multi-variate analysis to compare the differences in overall survival of the three treatment groups. The clock started at 30 days after relapse. A stepwise variable selection procedure was used for choosing adjusting variables. The final model was selected with adjustments for disease status prior to HCT, post-HCT maintenance TKI therapy, and year of HCT. Other variables considered but not selected in the final model included age, gender, country, KPS, anti-thymocyte globulin (ATG)/alemtuzumab, time from HCT to relapse, TBI usage, conditioning intensity, recipient CMV status, donor type, graft source, GVHD prophylaxis, and GVHD prior to the landmark analysis. Proportionality of all covariates were checked by using the time dependent covariates. Possible interactions between the main variable and other adjusted covariates were also examined. The effect of the main variable was tested at 0.05 significance level. Results were expressed as hazard ratios with 95% confidence intervals and p-values. Direct adjusted survival probabilities based on stratified Cox proportional hazards model were estimated at 1 year, 2 years and 3 years, with their point- wise 95% confidence intervals and p-values. Survival plots were generated from the final Cox model stratified on treatment of conditioning regime and weighted averages of covariate values using the pooled sample proportion as the weight functions. These adjusted probabilities estimate likelihood of outcomes in populations with similar prognostic factors. The analyses were conducted using SAS 9.4 TS1M4.

Study Endpoints

The primary endpoint was effect of salvage treatment starting at 30 days post HCT relapse on overall survival (OS) in the three treatment groups. Secondary endpoints examined included evaluation of cause of death, impact of disease status on overall survival, impact of maintenance on overall survival, and impact of GVHD on treatment effect.

Results

Patient-, Disease- and Transplantation-Related Variables

We identified 215 patients transplanted for CML between the years 2002 and 2014 who had received TKI prior to HCT and who had relapsed following their first allogeneic HCT. Table 1 displays patient-related, disease-related, and HCT-related baseline characteristics for the three groups, Combination arm, n = 48, Primary TKI, n = 128, and Primary DLI, n = 39. The completeness of follow-up, since 30 days post-HCT relapse in our defined population was 94% at 3 years. The median follow-up of survivors, 30 days post-HCT relapse was 58 months (6–132 months) for the Combination arm, 64 months (1–160months) for the Primary TKI arm and 46 month (3–91 months) for the Primary DLI. Other patient related factors such as age, gender, KPS status were well balanced between the groups. The HCT-CI was available for the years 2007–2014 (not available on CIBMTR form prior to 2007). Chronic phase disease status was more prevalent in those that received Primary DLI therapy compared to other groups, p =0.03.

The median time from HCT to relapse was slightly longer in the Primary TKI arm at 8 months (<1–107 months) compared to 6 months (<1–99 months) in the Combination arm, and 4 months (<1–70 months) in the Primary DLI arm, p = 0.04. The year of transplant differed, p < 0.01, as more patients that received primary DLI were treated prior to 2007. The majority of patients received peripheral blood as the graft source, this was greatest in the Combination arm at 85%, p = 0.01 (Table 1). A higher proportion in the Primary DLI arm received in vivo T cell depletion, compared to the other two groups, p = 0.006. It is noted that fewer patients that received maintenance therapy received a DLI as part of the salvage treatment, p=0.03, prompting planned inclusion of this variable in multivariate analysis below. Most common reported cause of death in all arms was relapse (Appendix 1).

In multivariate analysis (Table 3), as expected, the biggest impact on OS was disease status prior to HCT. As compared to those in chronic phase 1 (CP1), recipients that went to transplant in blast phase (BP) had a hazard ratio (HR) of 5.51 (95% confidence intervals [CI] 2.93–10.37; p<0.001) and patients in CP2 or higher had a HR 2.64 (95% CI 1.46–4.79; p = 0.001). Patients that received Primary DLI compared to Primary TKI had inferior survival HR 2.15 (95% CI 1.27–3.65; p = 0.004). Those who received Primary TKI had similar OS compared to those who received Combination therapy (p=0.81). In a sensitivity multivariate analysis, after controlling for how relapse was detected [clinical/hematologic vs. subclinical [molecular or cytogenetic]), TKI with or without DLI remained significantly associated with superior OS compared to DLI primary (p=0.003). Recipients who did not receive post-HCT maintenance had inferior OS with HR 2.00 (95% CI 1.21–3.31), p = 0.007. The presence of

acute GVHD prior to the landmark analysis was not significantly associated with post-relapse OS (p= 0.77).

Adjusted survival shows OS advantage of TKI use at 2 years, with OS of 65%, (95% CI: 0.53–0.77) in the Combination arm, 59%, (95% CI: 0.51–0.67) in the Primary TKI arm, and 41%, (95% CI: 0.27–0.55) in the Primary DLI arm (p=0.013) (Fig 1, Table 2).

Discussion

CIBMTR analyses show that patients with CML who relapse after HCT have the highest survival if treated with a TKI with or without immunotherapy with DLI. This study confirms that the major determining impact on survival after post-HCT relapse in CML is institution of TKI therapy. It further identifies DLI without TKI has inferior survival to any TKI containing therapy. This study did not aim to identify superiority of any particular TKI, however the most commonly used TKI at relapse was dasatinib.

The decision of which treatment modality to use at disease relapse can be difficult for clinicians as there are no large, prospective studies directing therapy. Each therapy comes with risks and benefits that must be weighed and the patient scenario at relapse may dictate which treatment strategy is used. Complications of DLI include GVHD, which can lead to morbidity and mortality, including increased use of immunosuppression followed by infection. A publication identified pre-DLI factors associated with prolonged survival in remission without secondary GVHD. The probability of survival in remission without secondary GVHD was highest (>50% at 5 years) when DLI were given beyond 1-year form HCT for molecular and/or cytogenetics CML relapse.[24] In the current study pre-relapse GVHD did not affect survival, however clinicians would be hesitant to use DLI in patients that had severe acute GVHD or ongoing chronic GVHD. DLI appears to be most effective in patients with CP, in our study there were relatively more patients with CP1 in the DLI arm.[25–26]

Imatinib has been studied in patients relapsing following HCT.[10] In one study of 128 patients, 50 patients had failed treatment with a DLI prior to starting imatinib therapy. Imatinib showed activity with complete cytogenetic response in 58% of patients in chronic phase (CP), 48% patients in accelerated phase (AP) and 22% of patients in blast crisis (BC). The 2-year survival in CP was 100%, 86% for AP and 12% for BC. Other studies have shown similar results.[11–16] Adverse effects of imatinib include neutropenia, thrombocytopenia, and gastrointestinal (GI) intolerance. Imatinib is most effective when patients are in CP.[10–13]

Imatinib combined with DLI has also been studied in 37 patients relapsing following HCT, where 13 patients received DLI only, 9 patients received imatinib only and 11 patients received DLI and imatinib combined; 4 patients received a DLI and imatinib, but not concurrently.[17] Ten of the 11 patients that received the combination achieved a molecular remission in 3 months, however only 2/22 patients that received either DLI only and imatinib only achieved a molecular remission at 3 months. The study concluded that imatinib and DLI are synergistic in the treatment of relapsed CML. A more recent study

included 71 patients at a single institution with CML that had undergone HCT comparing DLI, TKI or DLI + TKI for the treatment of relapsed CML post HCT. Out of the 71 patients, 45 patients relapsed following HCT and 40 patients went on to receive one of the 3 treatments following relapse. There was no statistically significant finding; however, the TKI-only group had the highest cumulative incidence of complete molecular remission and lowest cumulative incidence of death compared to DLI and TKI+DLI.[18] Shanavas et al analyzed 46 patients retrospectively who either received a DLI or TKI following relapse of HCT. This study found that TKI had improved OS with a HR of 37.4; 95% CI, 2.2–625.4, p = 0.01.[19]

We observed that patients had the highest OS when receiving a TKI with or without a DLI. There appears to be no added benefit to including DLI as part of the salvage therapy. Our study showed that disease status prior to HCT continues to confer poor prognosis. Interestingly, the presence of GVHD prior to the landmark analysis shows no impact on OS in this population of patients that had relapsed following HCT. Although the study is not designed to assess maintenance, as a covariate, maintenance TKI post-HCT was associated with superior post-relapse OS and this was independent of time from HCT to relapse. Post relapse overall OS was highest in HCT recipients who received a salvage TKI containing regimen compared to DLI primary salvage therapy. This data supports that despite use of TKI pre-transplantation and in maintenance therapy, TKI salvage therapy continues to provide significant OS following relapse in patients with CML following HCT. This data contradicts previously held thoughts that dosing of maintenance therapy might confer resistance at relapse and does not suggest that adding a DLI to TKI adds an improvement in OS, although the sample size is small.[27]

There are limitations to this study. While this is the largest study of this population to date, the decision made by the clinician to use one strategy vs. another was not captured, and even though multivariate regression analysis was performed to adjust for any captured baseline characteristics imbalances, it can only adjust for variables that are measured and captured. Furthermore, the registry did not collect dose quantification of DLI allowing better identification of immunotherapy thresholds/GVHD risk thresholds. There has been evidence linking increasing efficacy with increasing CD3+ cell dose, especially in patients with a molecular or cytogenetic relapse compared to a hematologic relapse, which could help better define dose requirements.[28] Our study included relapsed patients post HCT, given this design and selection procedure, some questions are not possible to address, such as why time to relapse was shorter in the Primary DLI arm; while we have adjusted for this factor, we are not able to answer the question since we did not include all patients (relapsed or not relapsed). Unfortunately, we did not have exact disease status (chronic, accelerated or blast phase) at the time of relapse to further define relapse severity. The registry does not collect data on responses to therapies given post HCT relapse, or the details of such therapies. Although these limitations are present, this study nevertheless represents a comprehensive picture of the current therapeutic landscape for CML therapy at relapse with current immunotherapy and TKI treatment options. While registration data is not all encompassing, it is exceedingly unlikely a clinical trial will be conducted to address this question for patients with CML.

In conclusion, our data suggest that TKI is the most effective treatment strategy at disease relapse following HCT for CML. Combination therapy of TKI plus DLI did not confer additional benefit, and DLI alone showed inferior OS when compared to TKI with or without a DLI.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights

- In the setting of CML relapse after HCT, TKI is an effective treatment strategy.
- DLI added to TKI does not appear to add benefit.
- DLI alone when compared to TKI alone has inferior survival in CML patients relapsing after HCT.

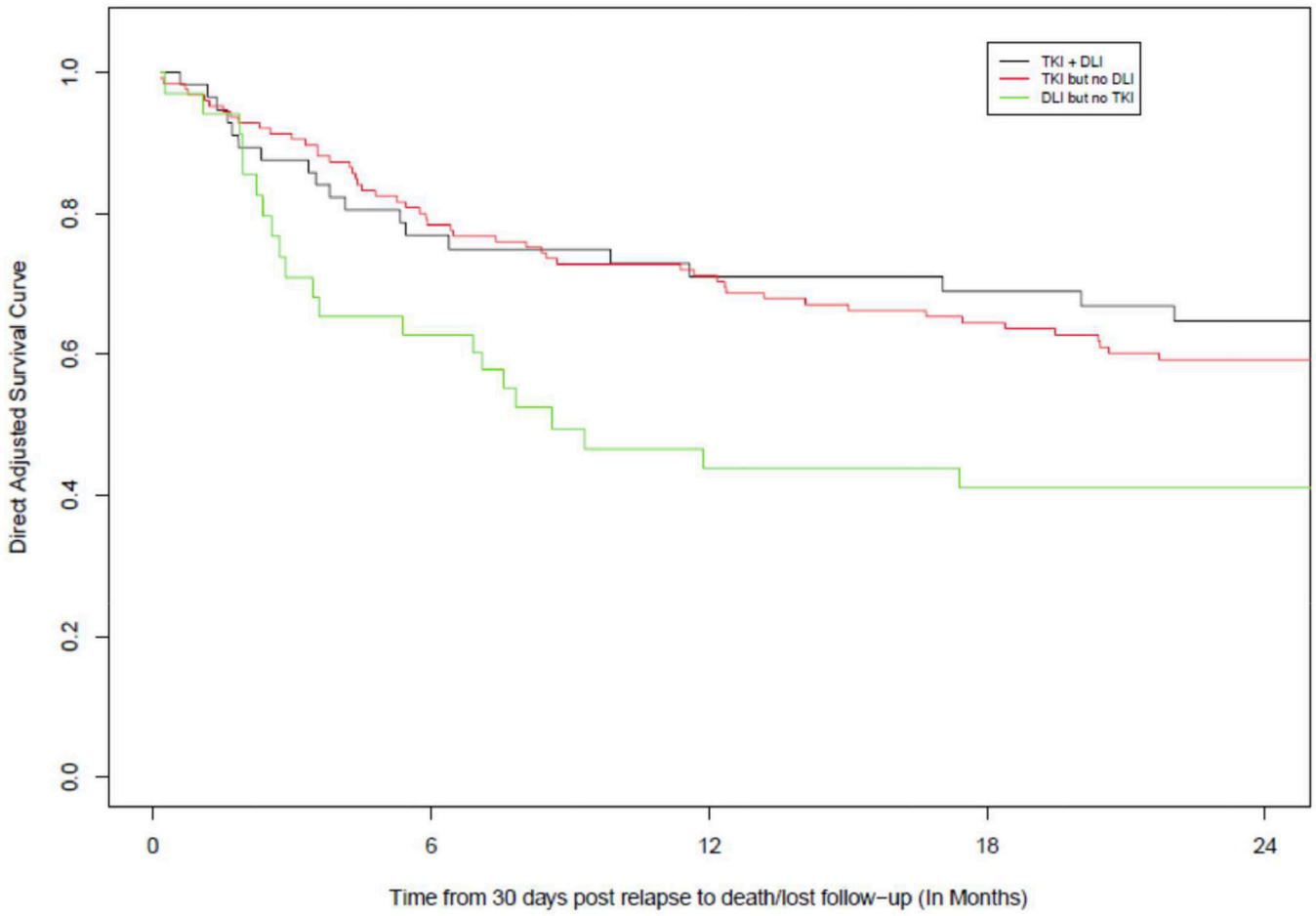

Figure 1.
Adjusted OS curves

Table 1.

Baseline Characteristics for Patients ≥ 18 years who Relapsed after HCT for CML, 2002–2014

Variable	TKI + DLI	TKI but no DLI	DLI but no TKI	P-value
Number of patients	48	128	39	
Number of centers	40	63	31	
Patient related				
Age, median (range), yrs	41 (22–66)	41 (18–73)	47 (19–61)	0.34
Gender				0.76
Female	18 (38)	51 (40)	13 (33)	
Karnofsky score at time of HCT				0.83
90–100	33 (69)	87 (68)	27 (69)	
HCT-CI				0.002
0	18 (38)	31 (24)	1 (3)	
1–2	6 (12)	19 (15)	1 (3)	
3+	7 (15)	17 (13)	5 (13)	
Missing/NA	17 (35)	61 (48)	32 (82)	
Pre-transplant disease related				
Disease status prior to HCT				0.03
CP1	14 (29)	39 (30)	16 (41)	
AP	7 (15)	17 (13)	11 (28)	
CP2+	15 (31)	33 (26)	4 (10)	
BP	7 (15)	12 (9)	6 (15)	
Hematologic CR	5 (10)	27 (21)	2 (5)	
Time from diagnosis to HCT (CP1), median (range), ms	14 (3–46)	14 (5–181)	24 (5–52)	0.66
Time from diagnosis to relapse, median (range), ms	31 (6–175)	38 (4–215)	38 (6–345)	0.70
Time from HCT to relapse, median (range), ms	6 (<1–99)	8 (<1–107)	4 (<1–70)	0.04
Transplant related				
Year of transplant				< 0.01
2002–2005	9 (19)	31 (25)	25 (64)	
2006–2009	28 (59)	63 (49)	11 (28)	
2010–2014	11 (22)	34 (26)	3(8)	
Graft source				0.01
Bone marrow	7 (15)	48 (38)	13 (33)	
Peripheral blood	41 (85)	80 (63)	26 (67)	
Recipient CMV status				0.85
Negative	18 (38)	52 (41)	18 (46)	
Positive	30 (63)	75 (59)	21 (54)	
Missing	0	1 (<1)	0	
Donor type				0.22
HLA-identical sibling	25 (52)	48 (38)	16 (41)	
Other related	2 (4)	8 (6)	0	
Well-matched unrelated	19 (40)	53 (41)	19 (49)	

Variable	TKI + DLI	TKI but no DLI	DLI but no TKI	P-value
Partially-matched unrelated	2 (4)	19 (15)	4 (10)	
Conditioning intensity				0.85
MAC - Chemo	18 (38)	56 (44)	17 (44)	
MAC - TBI	17 (35)	37 (29)	9 (23)	
RIC/NMA	13 (27)	34 (27)	13 (33)	
Missing	0	1 (<1)	0	
ATG/Alemtuzumab				0.006
ATG alone	12 (25)	28 (22)	16 (41)	
Alemtuzumab alone	4 (8)	2 (2)	4 (10)	
No ATG or Alemtuzumab	32 (67)	98 (77)	19 (49)	
GVHD prophylaxis				0.56
TAC based	27 (56)	77 (60)	17 (44)	
CSA based	16 (33)	39 (30)	18 (46)	
Post-HCT CY	2 (4)	7 (5)	2 (5)	
Other	3 (6)	3 (2)	2 (5)	
Missing	0	2 (2)	0	
Post-transplant disease related				
Post-HCT maintenance TKI therapy				0.03
No	35 (73)	87 (68)	35 (90)	
Yes	13 (27)	41 (32)	4 (10)	
Choice of treatment TKI therapy in response to relapse				
No TKI given	0	0	39	
IM + DA + NI	5 (10)	1 (<1)	0	
IM + DA	6 (13)	11 (9)	0	
IM + NI	3 (6)	3 (2)	0	
DA + NI	7 (15)	14 (11)	0	
IM	9 (19)	24 (19)	0	
DA	10 (21)	47 (37)	0	
NI	6 (13)	20 (16)	0	
Other	2 (4)	8 (6)	0	
Relapse assessment method				< 0.01
Hematologic/clinical	38 (79)	81 (63)	15 (38)	
FISH	3 (6)	2 (2)	1 (3)	
Conventional cytogenetics	2 (4)	9 (7)	9 (23)	
Molecular	4 (8)	22 (17)	2 (5)	
Assessment method unknown	1 (2)	14 (11)	12 (31)	
Distribution of GVHD prior to the Landmark Analysis				0.09
Patients that developed acute and chronic GVHD	3 (6)	19 (15)	1 (3)	
Patients that developed only acute GVHD	12 (25)	30 (23)	7 (18)	
Patients that developed only chronic GVHD	6 (13)	22 (17)	4 (10)	
Patients that did not develop GVHD	27 (56)	57 (45)	27 (69)	
Median follow-up of survivors (range) since 30-d post relapse, months	58 (6–132)	64 (1–160)	46 (3–91)	

Table 2.

Adjusted Survival Estimates for OS Since 30-d Post Relapse

Time	TKI + DLI	95% CI	TKI no DLI	95% CI	DLI no TKI	95% CI	P-value TKI + DLI vs. TKI only	P-value TKI +DL I vs. DLI only	P-value TKI only vs. DLI only
1 year	0.71	(0.60–0.82)	0.71	(0.64–0.79)	0.44	(0.29–0.59)	0.977	0.004	0.001
2 years	0.65	(0.53–0.77)	0.59	(0.51–0.67)	0.41	(0.27–0.55)	0.441	0.013	0.031
3 years	0.63	(0.51–0.75)	0.54	(0.46–0.62)	0.41	(0.27–0.55)	0.254	0.023	0.117

Table 3.

A Cox regression model was fitted for all eligible patients to evaluate the impact of main effect on overall survival since 30-d post relapse, while controlling for other risk factors.

Cox Model Estimates (N=215)				
Parameter	***N (N Event)***	***HR (%95 CI)***	***P-value***	***Overall P-value***
Disease status prior to HCT				
CP1 (reference)	69 (22)	1.00		**<.001**
AP	35 (16)	1.60 (0.83, 3.09)	0.157	
BP	25 (21)	5.51 (2.93, 10.37)	**<.001**	
CP2+	52 (31)	2.64 (1.46, 4.79)	**0.001**	
Hematologic CR	34 (18)	1.90 (0.94, 3.86)	0.075	
Main effect				
TKI + DLI (reference)	48 (24)	1.00		**0.011**
DLI but no TKI	39 (24)	2.28 (1.23, 4.24)	**0.009**	
TKI but no DLI	128 (60)	1.06 (0.65, 1.72)	0.813	
Post-HCT maintenance TKI Therapy				
Yes (reference)	58 (20)	1.00		**0.007**
No	157 (88)	2.00 (1.21, 3.31)	**0.007**	
Year of Transplant				
2002–2007 (reference)	110 (49)	1.00		**0.026**
2008–2014	105 (59)	1.68 (1.06, 2.64)	0.026	

* In addition, the other variables we considered but were not selected are age group, gender, country, KPS, ATG/Alemtuzumab, time from transplant to relapse, TBI given, conditioning intensity, recipient CMV status, donor type, graft source, GVHD Prophylaxis and GVHD prior to the landmark analysis.