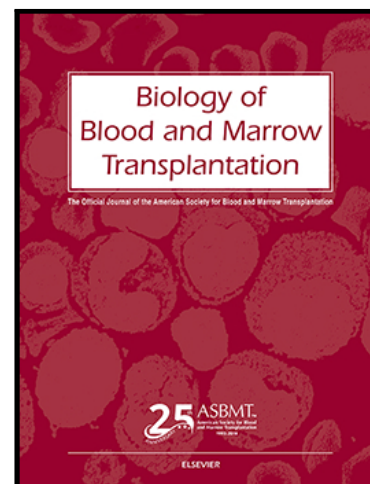


Maintenance tyrosine kinase inhibitors following allo-HCT for chronic myeloid leukemia: A CIBMTR Study



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PII: S1083-8791(19)30674-3
DOI: <https://doi.org/10.1016/j.bbmt.2019.10.017>
Reference: YBBMT 55765

To appear in: *Biology of Blood and Marrow Transplantation*

Received date: 18 July 2019
Accepted date: 16 October 2019

Please cite this article as: Zachariah DeFilipp , Richard Ancheta , Ying Liu , Zhen-Huan Hu , Robert Peter Gale , David Snyder , Harry C. Schouten , Matt Kalaycio , Gerhard C. Hildebrandt , Celalettin Ustun , Andrew Daly , Siddhartha Ganguly , Yoshihiro Inamoto , Mark Litzow , Jeffrey Szer , Mary Lynn Savoie , Nasheed Hossain , Mohamed A. Kharfan-Dabaja , Mehdi Hamadani , Ran Reshef , Ashish Bajel , Kirk R. Schultz , Shahinaz Gadalla , Aaron Gerds , Jane Liesveld , Mark B. Juckett , Rammurti Kamble , Shahrukh Hashmi , Hisham Abdel-Azim , Melhem Solh , Ulrike Bacher , Hillard Lazarus , Richard Olsson , Jean-Yves Cahn , Michael R. Grunwald , Bipin N. Savani , Jean Yared , Jacob M. Rowe , Jan Cerny , Naeem A. Chaudhri , Mahmoud Aljurf , Amer Beitinjaneh , Sachiko Seo , Taiga Nishihori , Jack W. Hsu , Muthalagu Ramanathan , Edwin Alyea , Uday Popat , Ronald Sobecks , Wael Saber , Maintenance tyrosine kinase inhibitors following allo-HCT for chronic myeloid leukemia: A CIBMTR Study, *Biology of Blood and Marrow Transplantation* (2019), doi: <https://doi.org/10.1016/j.bbmt.2019.10.017>

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Highlights

- Maintenance TKI therapy did not significantly impact allo-HCT outcomes for CML.
- Results were not modified by the status of disease prior to transplant.
- The optimal approach to TKI therapy after allo-HCT remains undetermined.

Journal Pre-proof

Title Page

Title: Maintenance tyrosine kinase inhibitors following allo-HCT for chronic myeloid leukemia: A CIBMTR Study

Running Head: TKI maintenance after HCT in CML

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Presentations: Preliminary results of this study were presented at the 2018 EBMT Annual Meeting in Lisbon, Portugal.

Disclaimers: None

Abstract

It remains unknown whether the administration of tyrosine kinase inhibitors (TKIs) targeting *BCR-ABL1* after allogeneic hematopoietic cell transplantation (HCT) is associated with improved outcomes for patients with chronic myeloid leukemia (CML). In this registry study, we analyzed clinical outcomes of 390 adult patients with CML

transplanted from 2007-2014 who received maintenance TKI following HCT (n=89) as compared to no TKI maintenance (n=301), as reported to the Center for International Blood and Marrow Transplant Research. All patients received TKI therapy prior to HCT. The majority of patients had disease beyond CP1 at HCT (n=240, 62%). The study was conducted as a landmark analysis, excluding patients that died, relapsed, had chronic graft-versus-host disease or were censored prior to Day 100 following HCT. Of the 89 patients receiving TKI maintenance, 77 (87%) received a single TKI while 12 (13%) received multiple sequential TKIs. The most common TKIs used for maintenance were dasatinib (n=50), imatinib (n=27) and nilotinib (n=27). As measured from Day 100, the adjusted estimates for 5-year relapse (maintenance, 35% vs. no maintenance, 26%; $p=0.11$), leukemia-free survival (LFS, maintenance, 42% vs. no maintenance, 44%; $p=0.65$) or overall survival (OS, maintenance, 61% vs. no maintenance, 57%; $p=0.61$) did not significantly differ between patients receiving TKI maintenance or no maintenance. These results remained unchanged in multivariate analysis and were not modified by the status of disease prior to transplant. In conclusion, our data did not demonstrate a significant impact of maintenance TKI therapy on clinical outcomes in a Day 100 landmark analysis. The optimal approach to TKI administration in the post-transplant setting in CML remains undetermined.

Keywords: chronic myeloid leukemia; tyrosine kinase inhibitor; allogeneic hematopoietic cell transplantation; maintenance;

Manuscript

Introduction

The introduction of tyrosine kinase inhibitors (TKIs) that target *BCR-ABL1* changed the therapeutic landscape for chronic myeloid leukemia (CML) and significantly improved clinical outcomes, with long term overall survival (OS) increasing from <20% to 80-90%.^{1, 2} Allogeneic hematopoietic cell transplantation (HCT) remains the only known curative treatment for CML. However, given the success of TKIs and the risks associated with transplant, HCT is currently reserved for patients with accelerated (AP) and blast phase (BP) CML and for TKI failure or intolerance in chronic phase (CP) disease.³ Despite the addition of TKIs prior to HCT, outcomes of patients receiving transplant have not significantly changed, with disease relapse being the leading cause of HCT failure.^{4, 5}

Maintenance therapy, defined as therapy initiated while the patient remains in complete remission, is a promising approach to reduce the incidence of relapse after HCT.⁶ The administration of TKIs as maintenance after allogeneic HCT for patients with high-risk Philadelphia chromosome-positive (Ph+) leukemia has been investigated in select studies⁷⁻¹⁰ and this approach is already being adopted into clinical practice.¹¹ While the use of maintenance TKI after HCT was associated with improved leukemia-free survival (LFS) and OS for patients with Ph+ acute lymphoblastic leukemia in an analysis from the European Group for Blood and Marrow Transplantation (EBMT)¹², larger studies investigating maintenance approaches in CML are lacking. Given the changing role of

HCT in the management of CML and the increasing utilization of TKIs in the post-transplant period, we sought to determine whether maintenance therapy with TKIs following HCT is associated with improved disease control and survival for patients with CML through analysis of the Center for International Blood and Marrow Research (CIBMTR) registry. We additionally sought to characterize the utilization and outcomes of HCT in the management of CML in a modern era of multiple available TKIs.

Methods

Data Sources

The CIBMTR is a combined research program of the Medical College of Wisconsin and the National Marrow Donor Program, which consists of a voluntary network of more than 450 transplantation centers worldwide that contribute detailed data on consecutive allogeneic and autologous transplantations to a centralized statistical center. Observational studies conducted by the CIBMTR are performed in compliance with all applicable federal regulations pertaining to the protection of human research participants. Protected health information issued in the performance of such research is collected and maintained in the CIBMTR's capacity as a Public Health Authority under the Health Insurance Portability and Accountability Act Privacy Rule.

The CIBMTR collects data, which include the following: age, sex, disease type, pre-transplant disease stage, date of diagnosis, graft type, conditioning regimen, post-transplant disease progression and survival, development of a new malignancy, and cause of death. Data are collected before transplantation, 100 days and 6 months after

transplantation, and annually thereafter or until death. The study protocol received a priori approval by the appropriate institutional review committee.

Study Population

The study population identified with the CIBMTR database included patients who underwent allogeneic HCT between 2007 and 2014. Patients identified were 18 years of age or older and underwent allogeneic HCT for CML for the first time. Donors were HLA-identical sibling donors, unrelated donors (URD), or umbilical cord blood. Patients who had not received TKIs prior to HCT and patients receiving therapies other than TKIs as maintenance following HCT were excluded. Patients who received ex-vivo T-cell depletion, CD34 selection, or post-transplant cyclophosphamide as graft-versus-host disease (GVHD) prophylaxis were also excluded. Published experiences with maintenance TKIs have reported a median initiation date between Day 30 and Day 100 following allogeneic HCT.⁷⁻¹¹ Thus, we chose to conduct this study as a landmark analysis that excluded patients that died, relapsed, had cGVHD or were lost to follow up prior to Day 100 post-HCT.

Variables Included in the Analysis

The data analysis included patient-related variables were the age at HCT, sex, and Karnofsky performance status (KPS). Disease-related variables included the disease status at transplant (CP1 vs. CP2+ vs. AP vs. BP). Transplant-related variables included conditioning regimen intensity (as defined by the CIBMTR),¹³ donor-recipient HLA-match (HLA-identical sibling, well matched URD, partially matched URD, mismatched

URD),¹⁴ GVHD prophylaxis, and the time period in which the transplant was performed (2007-2008, 2009-2010, 2011-2012, 2013-2014). Maintenance therapy was determined based on data recorded from the Day 100 post-HCT disease specific form, which included the choice of TKI but not the date of initiation, dose or the duration of maintenance therapy. Relapse was defined by report of molecular, cytogenetic, and/or hematologic disease post-HCT.

Study Endpoints and Statistical Analysis

This was a retrospective cohort landmark study from 100 days after HCT to compare outcomes of patients transplanted with CML who received maintenance TKI therapy to controls (no maintenance therapy). The primary aim was to compare LFS, and the secondary aim was to compare the OS, chronic GVHD, TRM and relapse between these 2 groups. All the outcomes are time to events with the starting time at 100 days after transplantation.

Descriptive statistics were calculated for all variables. A univariate analysis was performed with the Kaplan-Meier estimates to compute OS and LFS rates. Log-rank tests were used to measure the differences of OS and LFS between the treatment groups. Chronic GVHD, TRM and relapse rates were estimated with the cumulative incidence functions with consideration of competing risks. Gray's test was performed to compare the differences of cumulative incidence functions between treatment groups.

Multivariate Cox proportional hazards regression models for all the endpoints (LFS, OS, relapse TRM, and cGVHD) were used to compare the treatment groups. The assumption of proportional hazards for each factor in the Cox model was tested using time-dependent covariates. There is no variable violating the proportional hazard assumption in this study. Stepwise selection was used to identify significant covariates that influenced outcomes to be included in the final model to get the adjusted treatment effects. The set of adjusting variables for each outcome was decided separately by stepwise selection with inclusion criteria at 0.05. Statistical significance of the main effects was tested with level 0.01 accounting for multiple comparisons across the endpoints. Potential interactions between the main effect and significant adjusting covariates and between main effect and donor type were tested and there are no significant interactions at level of 0.01.

Adjusted survival curves and cumulative incidence curves were generated stratified on the treatment groups and weighted averages of covariate values using the pooled sample proportion as the weight function. These adjusted curves represent likelihood of outcomes in populations with similar prognostic factors.

Results

Patient and Transplant Characteristics

In total, 572 patients with CML were initially identified according the defined study population (**Supplemental Tables 1a and 1b**). Of this, 182 patients were excluded as part of the Day 100 landmark criteria (**Figure 1, Supplemental Table 2**), leaving 390

eligible patients for the analysis. Two cohorts were identified: 1) those receiving post-HCT maintenance TKI therapy (n=89), and 2) those not receiving post-HCT maintenance TKI therapy (n=301). Patient characteristics are outlined in **Table 1**. The median follow-up for survivors after Day 100 post-HCT was 61 months (range, 7-97) in the maintenance TKI cohort and 68 months (range, 2-98) in the no maintenance cohort. There was no difference in median age, sex, or KPS at HCT between the two groups. Overall, the majority of patients had disease beyond CP1 at HCT (n=240, 62%). Disease status prior to HCT differed between the two groups, with a higher percentage of patients CP2+ being in the maintenance cohort and a higher percentage of patients with CP1 in the no maintenance cohort ($p < 0.001$). Transplant characteristics were similar between the two cohorts in regards to the most common donor types (HLA matched siblings and unrelated donors), graft source (peripheral blood stem cells), conditioning intensity (myeloablative) and GVHD prophylaxis (calcineurin inhibitor plus methotrexate). The administration of donor lymphocyte infusions as prophylaxis or for mixed chimerism was rare (TKI maintenance, n=0; no TKI maintenance, n=4).

TKI therapy prior to HCT

All patients in this analysis received TKI therapy prior to transplant, with the majority of patient receiving multiple TKIs in both the maintenance (67%) and non-maintenance cohorts (75%). The most commonly used TKIs prior to HCT were imatinib (n=362), dasatinib (n=276), and then nilotinib (n=125). The duration of TKI therapy prior to HCT, as well as the reason for multiple TKI use (resistance, intolerance or other), were unavailable.

Maintenance TKI therapy after HCT

Eighty-nine patients (23%) received TKI maintenance therapy after HCT (**Table 2**). Of these, 77 (87%) received a single TKI and 12 (13%) received multiple TKIs. In the majority of cases (n=72, 81%), a different TKI was administered post-HCT as compared to pre-HCT. The most common TKIs used for maintenance were dasatinib (n=50), imatinib (n=27), and nilotinib (n=27). The start date and duration of maintenance TKI therapy were unavailable.

OS

We observed no significant difference in the adjusted 2-year and 5-year OS from Day 100 between the two cohorts (2-year: 76% (95% confidence interval [CI], 68-85%) for the maintenance cohort, 69% (95% CI, 64-82%) for the no maintenance cohort (p=0.15); 5-year: 61% (95% CI, 50-72%) for the maintenance cohort, 57% (95% CI, 52-67%) for the no maintenance cohort (p=0.61)) (**Figure 2**). The leading cause of death in the maintenance cohort was disease relapse, while the leading cause of death in the no maintenance cohort was GVHD (**Supplemental Table 3**). In the multivariate analysis (**Table 3**), BP disease status prior to HCT, CP2+ disease status prior to HCT, cord blood graft source, and peripheral blood graft source were independent adverse risk factors for OS (hazard ratio [HR] for BP, 2.4 (reference, CP1): 95% CI, 1.3-4.3, p=0.005; HR for CP2+, 1.6 (reference, CP1): 95% CI, 1.1-2.4, p=0.013; HR for cord blood, 2.6 (reference, bone marrow): 95% CI, 1.4-4.7, p=0.002; HR for peripheral blood, 2.1 (reference, bone marrow): 95% CI, 1.3-3.4, p=0.004). Maintenance TKI therapy was not

a risk factor for OS (HR 0.7 (reference, no maintenance): 95% CI, 0.5-1.1, $p=0.078$).

LFS

We observed no significant difference in the adjusted 2-year and 5-year LFS from Day 100 between the two cohorts (2-year: 56% (95% CI, 45-66%) for the maintenance cohort, 56% (95% CI, 50-61%) for the no maintenance cohort ($p=0.95$); 5-year: 42% (95% CI, 31-53%) for the maintenance cohort, 44% (95% CI, 39-47%) for the no maintenance cohort ($p=0.65$) (**Figure 3**). In the multivariate analysis (**Table 3**), BP disease status prior to HCT, CP2+ disease status prior to HCT, and age ≥ 60 were independent adverse risk factors for LFS (HR for BP, 1.8 (reference, CP1): 95% CI, 1.0-3.1, $p=0.039$; HR for CP2+, 1.7 (reference, CP1): 95% CI, 1.2-2.4, $p=0.003$; HR for age ≥ 60 , 2.3 (reference, age 18-29): 95% CI, 1.3-3.9, $p=0.004$). Maintenance TKI therapy was not a risk factor for LFS (HR 0.9 (reference, no maintenance): 95% CI, 0.6-1.2, $p=0.356$).

Relapse

The most common presentation of relapsed disease in both cohorts were hematologic relapses (TKI maintenance, $n=22$, 69%; no TKI maintenance, $n=50$, 68%). We observed an increased adjusted incidence of relapse at 2-years from Day 100 when comparing the TKI maintenance cohort to the no maintenance cohort (2-year: 33% (95% CI, 23-43%) vs. 22% (95% CI, 17-38%), $p=0.04$). However, no significant difference was observed in 5-year outcomes (35% (95% CI, 25-45%) for the maintenance cohort, 26% (95% CI, 21-40%) for the no maintenance cohort ($p=0.11$)) (**Figure 4**). In the

multivariate analysis (**Table 3**), KPS <90 was an independent adverse risk factors for relapse (HR for KPS <90, 2.0 (reference, KPS 90-100); 95% CI, 1.3-3.0, $p=0.001$). Maintenance TKI therapy was not a risk factor for relapse (HR 1.4 (reference, no maintenance); 95% CI, 0.9-2.1, $p=0.170$).

TRM

We observed a lower adjusted incidence of TRM at 1-year from Day 100 when comparing the TKI maintenance cohort to the no maintenance cohort (1-year: 8% (95% CI, 2-13%) vs. 19% (95% CI, 14-24%) $p=0.004$). However, no significant difference was observed in 5-year outcomes (23% (95% CI, 13-32%) for the maintenance cohort, 30% (95% CI, 25-28%) for the no maintenance cohort ($p=0.19$)). In the multivariate analysis (**Table 3**), cord blood graft source and peripheral blood graft source were independent adverse risk factors for TRM (HR for cord blood, 2.7 (reference, bone marrow); 95% CI, 1.2-5.8, $p=0.012$; HR for peripheral blood, 2.4 (reference, bone marrow); 95% CI, 1.3-4.4, $p=0.006$). Maintenance TKI therapy was not a risk factor for TRM (HR 0.7 (reference, no maintenance); 95% CI, 0.4-1.1, $p=0.130$).

Chronic GVHD

We observed no significant difference in the adjusted 2-year cGVHD from Day 100 between the two cohorts (60% (95% CI, 50-69%) for the maintenance cohort, 62% (95% CI, 57-65%) for the no maintenance cohort ($p=0.67$)). In the multivariate analysis (**Table 3**), peripheral blood graft source was an adverse risk factor for cGVHD (HR for peripheral blood, 2.0 (reference, bone marrow); 95% CI, 1.4-2.8, $p<0.001$) and

cyclosporine based GVHD prophylaxis and KPS <90 were independent protective factors against cGVHD (HR for cyclosporine based GVHD prophylaxis, 0.6 (reference, tacrolimus based GVHD prophylaxis); 95% CI, 0.4-0.8, $p=0.003$; HR for KPS <90, 0.6 (reference, KPS 90-100); 95% CI, 0.4-0.8, $p<0.001$). Maintenance TKI therapy was not a risk factor for cGVHD (HR 0.8 (reference, no maintenance); 95% CI, 0.6-1.1, $p=0.124$).

Subgroup analysis investigating disease status prior to HCT

We specifically investigated the interaction of the main effect (TKI maintenance or no maintenance) on the primary outcomes of the study (LFS), according to disease status prior to HCT. We observed no differential impact of maintenance TKI on LFS (as measured from Day 100 post HCT) based on disease status prior to HCT (Figure 5).

We additionally performed a sensitivity analysis, repeating the above multivariate analysis after removing patients with CP1 disease. We observed no differential impact of maintenance TKI on major clinical outcomes (OS, LFS, relapse, TRM, chronic GVHD) when analyzing patients with disease beyond CP1 at HCT (**Supplemental Table 4**).

Discussion

In this retrospective registry analysis, we sought to investigate the practice of TKI maintenance therapy following HCT in patients with CML. Our results confirm that in a modern era of TKI therapy, HCT remains a curative option for patients with CML, with

encouraging survival. We report that the maintenance approach has not been universally adopted, as only 23% of patients received TKI maintenance in this data set. In a landmark analysis from Day 100, we did not demonstrate a benefit in 5-year clinical outcomes (LFS, OS, relapse, TRM or cGVHD) with the use TKI maintenance as compared to no maintenance. While TKI maintenance was associated with a higher incidence of relapse and lower incidence of TRM at earlier time points as compared to the no maintenance cohort, these findings did not maintain significance when analyzing 5-year outcomes or when evaluating the impact of maintenance therapy in the multivariate Cox proportional hazards regression model. The results of this study characterize the clinical outcomes of patients receiving TKI maintenance and question the broad application of this approach to all patients with CML. The impact of maintenance TKI did not differ based on disease status prior to HCT, although we acknowledge that additional differences in disease risk, as well as physician intent to initiate maintenance therapy, could not be accounted for with this registry analysis. Nevertheless, we believe the results of this study to be important to clinical practice, given the potential toxicities and costs associated with maintenance therapy.

We believe that a number of important factors influenced the outcomes of this study. First, we used a landmark analysis from Day 100 following HCT to calculate all follow up and outcomes. Evaluation of maintenance therapies is often associated with inherent selection bias, as patients must be alive and usually without early major HCT complications (relapse, GVHD, infection, organ toxicity), which can confound clinical perception of the clinical impact of maintenance approaches. By conducting a landmark

analysis, we excluded patients with early death, relapse, and chronic GVHD, and hereby we tried to correct for this bias. However, we postulate that this study design may have also influenced the findings at earlier time points of higher relapse and less TRM with TKI maintenance, as an increased number of relapses and deaths prior to Day 100 were excluded from the no maintenance cohort. Another major factor to consider is the heterogeneity in disease risk and its influence on clinician decision to initiate TKI maintenance. While we observed differences in disease status prior to transplant, we lack additional data on disease risk and TKI sensitivity (including ABL1 domain mutations). We also do not know the reason for the initiation of TKI maintenance or whether patients in the no maintenance cohort were originally intended to receive maintenance. While we observed no significant impact of TKI maintenance on clinical outcomes in this study, we acknowledge that unmeasured cofounders exist that could potentially influence the outcomes of this study. Finally, the majority of patients in this study received myeloablative conditioning, which has been associated with lower rates of relapse early after HCT when compared with reduced intensity conditioning.¹⁵ This conditioning intensity may have influenced clinician decision to initiate post-HCT maintenance therapy. Given the higher risk for relapse early after HCT with RIC, this may be a population in which TKI maintenance may be of more importance until the full potency of GVL is in effect.

A small number of studies have investigated the use of prophylactic post-transplant maintenance TKIs in patients with Ph+ leukemia. Two early prospective trial of imatinib maintenance in the first year following allogeneic HCT found this approach to be

feasible and associated with low rates of relapse.^{7, 8} As many patients undergoing allogeneic HCT have failed first-line TKIs, there is great interest in the post-HCT use of later generation TKIs. However, the later generation TKIs in particular have been associated with increased toxicities. A phase I/II study investigating nilotinib after allogeneic HCT in 16 patients with high-risk Ph+ leukemia reported 2-year OS and progression-free survival of 69% and 56%, respectively.⁹ In this study, 38% of patients had to discontinue therapy because of toxicities, which were predominantly gastrointestinal or hepatic. In a separate phase I/II study, only 32.5% of patients eligible for nilotinib maintenance at engraftment were able to complete the intended 1 year of therapy because of early relapse, toxicities or confounding post-HCT complications.¹⁰ Toxicities can limit duration of TKI maintenance, which is thought to impact the effectiveness of this approach although no studies to date have addressed a minimum or optimal duration of maintenance therapy. No previous registry studies have investigated maintenance TKI use in CML, but in an EBMT analysis of Philadelphia chromosome-positive acute lymphoblastic leukemia, the use of maintenance TKI post-transplant was identified to be a significant factor for improved LFS (HR=0.44, P=0.002) and OS (HR=0.42, P=0.004) and lower relapse incidence (HR=0.40, P=0.01).¹² Patients with CML undergoing allogeneic HCT may have increased heterogeneity in disease risk and TKI sensitivity (possibly driven by additional mutations outside of *BCR-ABL1*), which may have limit the extent to which registry analyses are able to detect an impact of TKI maintenance in CML as compared to Ph+ ALL.

The current study has additional limitations. A significant limitation was the relatively small size of the cohort of TKI maintenance, although given the current indications for HCT in CML, our study represents a comprehensive study cohort. Given the limits of the data collected in regards to TKI maintenance, we lack information on the start date, the dose, the duration of therapy, and the reason for which TKI maintenance was stopped. We acknowledge these limitations restrict our ability to assess the impact of this approach, as TKI maintenance therapy may be discontinued after short periods of time due to TKI intolerance or other transplant complications.¹¹ As a result, we analyzed clinical outcomes according to the initiation of maintenance TKI therapy, as reported to the CIBMTR registry, and acknowledge that additional data about maintenance therapy could provide insights into its clinical impact. We also lack data in regards to financial burden of maintenance therapy and as well as late effects, two important factors that can impact quality of life for patients. Finally, this study captures transplants performed during an era of expanding TKI agents. Thus, patients in the earlier years of the study with resistance or intolerance to imatinib or dasatinib prior to HCT may not have had appropriate TKIs with which to continue maintenance. Currently, with five available TKIs targeting *BCR-ABL 1*, there is no clear optimal choice of TKI following HCT.

In conclusion, the broad application of maintenance TKI following allogeneic HCT does not seem to be of benefit for patients with CML. It remains unclear if there are subpopulations of patients with CML who may benefit from TKI maintenance. We believe that the choice to initiate TKIs after allogeneic HCT should be an individualized decision, based upon patient-, disease-, and transplant-related factors.

Acknowledgements

This study is dedicated in the memory of Dr. Hanna Jean Khoury, who provided mentorship during the development of the study concept and the early phases of the study design.

Authorship

Z.D., R.A., Y.L., Z.-H.H., R.S., and W.S. designed the study, analyzed data, and wrote the manuscript. Writing Committee members (includes all authors listed on the title page) designed the study and wrote the manuscript.

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Figure Legend

Figure 1. Study flow diagram.

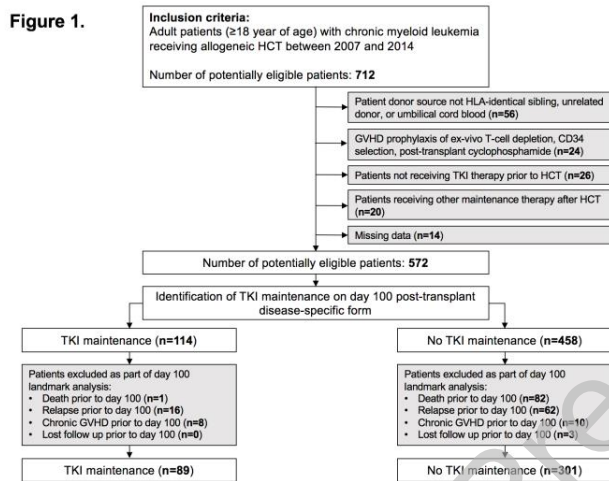


Figure 2. Kaplan-Meier curve of overall survival according to post-HCT maintenance therapy with tyrosine kinase inhibitors.

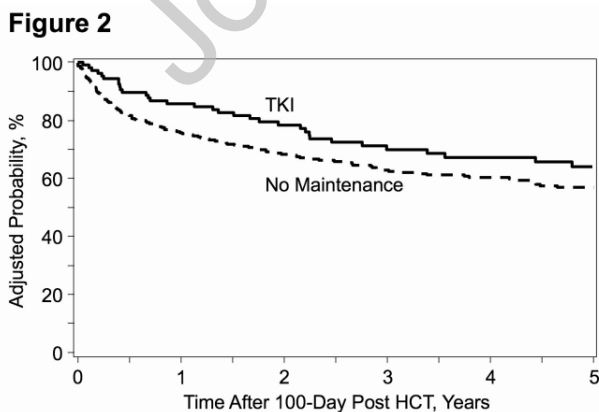


Figure 3. Kaplan-Meier curve of leukemia-free survival according to post-HCT maintenance therapy with tyrosine kinase inhibitors.

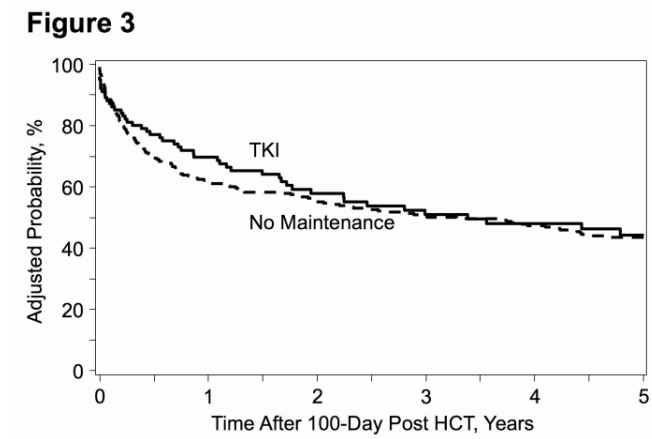


Figure 4. Cumulative incidence curve of relapse according to post-HCT maintenance therapy with tyrosine kinase inhibitors.

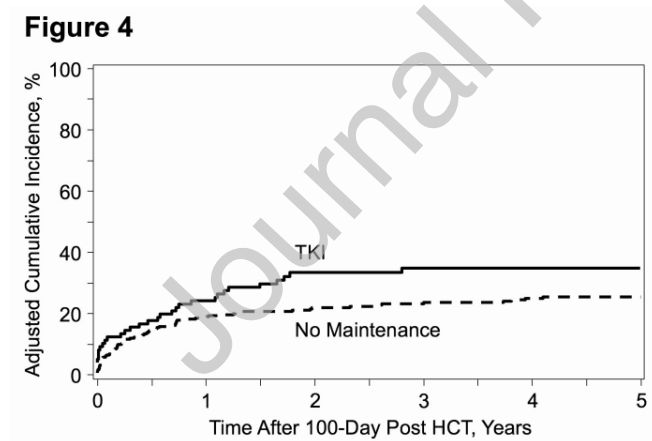
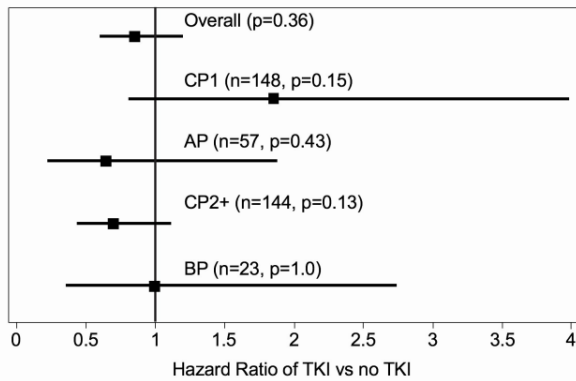


Figure 5. Forest plot of leukemia free survival according to disease status prior to HCT.**Figure 5****Table 1. Patient, disease, and transplant characteristics.**

Variable	Post-HCT maintenance TKI	No post-HCT maintenance TKI	p-value
Number of patients	89	301	
Number of centers	45	101	
Age, median (range), y	46 (19-64)	44 (18-76)	0.59
Sex, n (%)			0.23
Male	56 (63)	168 (56)	
Female	33 (37)	133 (44)	
KPS at HCT, n (%)			0.91
≥90	64 (72)	218 (72)	
<90	23 (26)	74 (25)	
Missing	2(2)	9(3)	
Number of TKI therapies prior to HCT, n (%)			
1	29 (33)	76 (25)	
>1	60 (67)	225 (75)	
TKI therapies prior to HCT, n (%)			
Imatinib	77 (87)	285 (94)	
Dasatinib	63 (71)	213 (71)	
Nilotinib	25 (28)	100 (33)	
Ponatinib	0	1 (<1)	
Disease status prior to HCT, n (%)			<0.001
CP1	13 (15)	137 (46)	
CP2+	53 (60)	95 (32)	
AP	12 (13)	48 (16)	
BP	9 (10)	14 (5)	
Missing	2 (2)	7 (2)	
Graft source			0.69

Bone marrow	16 (18)	66 (22)	
Peripheral blood	62 (70)	196 (65)	
Cord blood	11 (12)	39 (13)	
Donor type, n (%)			0.42
HLA-identical sibling	31 (35)	96 (32)	
Well matched URD	32 (36)	130 (43)	
Partially matched URD	15 (17)	33 (11)	
Mismatched URD	0	3 (<1)	
Cord blood	11 (12)	39 (13)	
Conditioning regimen intensity, n (%)			0.51
MAC	76 (85)	250 (83)	
RIC	8 (9)	40 (13)	
NMA	5 (6)	10 (3)	
Missing	0	1 (<1)	
GVHD prophylaxis, n (%)			0.65
CNI + MTX	61 (69)	182 (60)	
CNI + MMF	23 (26)	80 (26)	
Other	5 (6)	39 (13)	
Year of HCT, n (%)			0.01
2007-2008	19 (21)	120 (40)	
2009-2010	45 (51)	112 (37)	
2011-2012	9 (10)	22 (7)	
2013-2014	16 (18)	47 (16)	
Median follow up of survivors after Day 100 post-HCT (range), m	61 (7-97)	68 (2-98)	

Abbreviations:

AP: accelerated phase; BP: blast phase; CNI: calcineurin inhibitor; CP: chronic phase; CR: complete remission; HCT: hematopoietic cell transplantation; KPS: Karnofsky performance status; m: months; MAC: myeloablative conditioning; MMF: mycophenolate mofetil; MTX: methotrexate; n: number; NMA: non-myeloablative conditioning; RIC: reduced intensity conditioning; TKI: tyrosine kinase inhibitor; URD: unrelated donor; y: year;

Table 2. Characteristics of post-transplant TKI maintenance.

Variable	Value
Number of patients receiving maintenance TKI therapy	89
Number of TKI maintenance therapies, n (%)	
1	77 (87)
>1	12 (13)
Same TKI given pre-HCT and post-HCT	

No	72 (81)
Yes	17 (19)
TKIs used as maintenance therapies, n	
Dasatinib	50
Imatinib	27
Nilotinib	27

Abbreviations

HCT: hematopoietic cell transplantation; n: number; TKI: tyrosine kinase inhibitor;

Table 3. Day 100 landmark multivariate analyses of clinical outcomes.*

	Chronic GVHD	TRM	Relapse	LFS	OS
Disease status					
CP1 (reference)	--	--	--	--	--
AP	--	--	--	1.3 (0.8-2.0), p=0.284	1.0 (0.6-1.7), p=0.901
BP	--	--	--	1.8 (1.0-3.1), p=0.039	2.4 (1.3-4.3), p=0.005
CP2+	--	--	--	1.7 (1.2-2.4), p=0.003	1.6 (1.1-2.4), p=0.013
Graft Source					
Bone marrow (reference)	--	--	--	--	--
Cord blood	1.0 (0.6-1.6), p=0.848	2.7 (1.2-5.8) p=0.012	--	--	2.6 (1.4-4.7), p=0.002
Peripheral blood	2.0 (1.4-2.8), p<0.001	2.4 (1.3-4.4), p=0.006	--	--	2.1 (1.3-3.4), p=0.004
GVHD prophylaxis					
Tacrolimus +/- others (reference)	--	--	--	--	--
Cyclosporine +/- others	0.6 (0.4-0.8), p=0.003	--	--	--	--
Others	0.5 (0.1-2.0), p=0.336	--	--	--	--
Age Group					
18-29 (reference)	--	--	--	--	--
30-39	--	--	--	1.0 (0.6-1.5), p=0.849	--
40-49	--	--	--	1.2 (0.8-1.9), p=0.353	--
50-59	--	--	--	1.0 (0.6-1.5), p=0.944	--
≥60	--	--	--	2.3 (1.3-3.9), p=0.004	--

Karnofsky score					
90-100 (reference)	--	--	--	--	--
<90	0.6 (0.4-0.8), p<0.001	--	2.0 (1.3-3.0), p=0.001	1.4 (1.0-1.9), p=0.058	--
Maintenance therapy					
No (reference)	--	--	--	--	--
Yes	0.8 (0.6-1.1), p=0.124	0.7 (0.4-1.1), p=0.130	1.4 (0.9-2.1), p=0.170	0.9 (0.6-1.2), p=0.356	0.7 (0.5-1.1), p=0.078

**Hazard ratios presented with 95% Confidence Interval in parenthesis*

Abbreviations

AP: accelerated phase; BP: blast phase; CP: chronic phase; CR: complete remission; GVHD: graft-versus-host disease; LFS: leukemia-free survival; OS: overall survival; TRM: transplant-related mortality;