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RESEARCH ARTICLE

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Allogeneic hematopoietic cell transplantation in patients with chronic phase chronic myeloid leukemia in the era of third generation tyrosine kinase inhibitors: A retrospective study by the chronic malignancies working party of the EBMT

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Abstract

Following the introduction of tyrosine kinase inhibitors (TKI), the number of patients undergoing allogeneic hematopoietic cell transplantation (allo-HCT) for chronic phase (CP) chronic myeloid leukemia (CML) has dramatically decreased. Imatinib was the first TKI introduced to the clinical arena, predominantly utilized in the first line setting. In cases of insufficient response, resistance, or intolerance, CML patients can subsequently be treated with either a second or third generation TKI. Between 2006 and 2016, we analyzed the impact of the use of 1, 2, or 3 TKI prior to allo-HCT for CP CML in 904 patients. A total of 323-, 371-, and 210 patients had 1, 2, or 3 TKI prior to transplant, respectively; imatinib ($n = 778$), dasatinib ($n = 508$), nilotinib ($n = 353$), bosutinib ($n = 12$), and ponatinib ($n = 44$). The majority had imatinib as first TKI ($n = 747$, 96%). Transplants were performed in CP1, $n = 549$, CP2, $n = 306$, and CP3, $n = 49$. With a median follow-up of 52 months, 5-year OS for the entire population was 64.4% (95% CI 60.9–67.9%), PFS 50% (95% CI 46.3–53.7%), RI 28.7% (95% CI 25.4–32.0%), and NRM 21.3% (95% CI 18.3–24.2%). No difference in OS, PFS, RI, or NRM was evident related to the number of TKI prior to allo-HCT or to the type of TKI (p = ns). Significant factors influencing OS and PFS were > CP1

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For affiliation refer to page 120

versus CP1 and Karnofsky performance (KPS) score > 80 versus ≤80, highlighting CP1 patients undergoing allo-HCT have improved survival compared to >CP1 and the importance of careful allo-HCT candidate selection.

1 | INTRODUCTION

Following the introduction of tyrosine kinase inhibitors (TKI) in the early 2000s, the use of allogeneic hematopoietic cell transplantation (allo-HCT) for chronic myeloid leukemia (CML) has dramatically decreased.[1–3] Imatinib was the first TKI introduced and is mostly used in the first line setting. However, although response rates are impressive, after 11 years of treatment only 48% of patients remained on imatinib.[1] Therefore, more than 50% of patients will need another therapy, due either to insufficient response, resistance, or intolerance. Those CML patients can then be treated with a second or third generation TKI, many gaining adequate response.[4,5] Approximately half of this group will achieve or regain remission on one of the second generation TKI (2GTKI), bosutinib, dasatinib, nilotinib, or third generation TKI (3GTKI) ponatinib which is the only TKI that is effective against the T315I mutation.[4–7] The efficacy of 2GTKI has led to their use as first line therapy and recently completed phase III studies suggest that approximately 80% of patients will achieve complete cytogenetic remissions within the first year, compared to only 65% on imatinib.[8,9] Based on these results, dasatinib and nilotinib have both been licensed for use in newly diagnosed patients.

However, allo-HCT remains the therapy of choice for advanced phase CML as well as for those with chronic phase (CP) disease who fail to respond to several TKI, develop TKI-resistant mutations, loose an established response, provide evidence of clonal disease evolution, and/or are intolerant of the drug. The time to proceed to allo-HCT, however, remains controversial. In the present study, we therefore analyzed the impact of the use of 1, 2, or 3 TKI prior to allo-HCT on transplant outcomes in patients undergoing first allo-HCT for CML in CP.

2 | METHODS

This was a retrospective, multicenter, registry-based analysis approved by the Chronic Malignancies Working Party of the EBMT. The EBMT is a non-profit, scientific society representing more than 600 transplant centers mainly in Europe. EBMT centers commit to obtain informed consent according to the local regulations applicable at the time in order to report pseudonymized data stored in a central database. We selected patients from this database who underwent first allo-HCT for CML in CP between 2006 and 2016 and had information on the TKI received prior to transplantation. Only patients who had received 1, 2, or 3 TKI's prior to the allo-HCT were included. Other criteria of inclusion were: 18 years of age or more at time of allo-HCT, peripheral blood (PB) or bone marrow (BM) as stem cell source, myeloablative conditioning (MAC) or reduced intensity conditioning (RIC) and having received a graft from a matched related donor (MRD), a mismatched related donor (MMRD), or a matched or mismatched unrelated donor (MUD or MMUD). Thus, haplo-identical donors were not included. It was our hypothesis that the number of lines of TKIs used before allogeneic stem cell transplantation may have a negative impact on the overall outcome. Thus, the primary objective of the study was to assess the impact of the number of TKIs and type of TKI combination consecutively received on overall survival (OS) after allo-HCT. Secondary endpoints were progression free survival (PFS), relapse incidence (RI), non-relapse mortality (NRM), and cumulative incidence of graft versus host disease (GvHD).

2.1 | Statistical analysis

2.1.1 | Relapse

Relapse was classified as molecular (i.e., any level of *BCR-ABL* transcripts detected by quantitative reverse transcription–polymerase chain reaction [RT-PCR] in two consecutive tests performed over a minimum of 4 weeks), cytogenetic (i.e., reappearance of one or more Philadelphia chromosome–positive [Ph^+] metaphases at bone marrow cytogenetics), or hematologic (i.e., presence of peripheral blood leukocytosis accompanied by a hypercellular bone marrow with presence of Ph^+ chromosome on cytogenetic analysis) in accordance with previous reports.[10–12] The phase of CML was classified in accordance with the standard criteria proposed by Speck et al.[13]

2.1.2 | Endpoints

OS was defined as the time from allo-HCT to death from any cause. PFS was defined as the time between allo-HCT and relapse/progression of disease or death, whichever occurred first. Patients still alive were censored at their last follow-up.

The median follow-up from transplant was calculated using the reverse Kaplan–Meier estimator.[14] All *p*-values shown are from two-sided tests and the reported confidence intervals (CI) refer to 95% boundaries, a *p*-value < .05 was regarded as statistically significant.

Patients' characteristics between groups were compared using the χ^2 test for categorical variables and the Kruskal–Wallis test for continuous data. Probabilities of OS and PFS were computed using the Kaplan–Meier estimator and compared by log-rank test. The crude cumulative incidence estimator and Gray's test were used for competing events (RI and NRM; chronic GvHD, death before chronic GvHD and a subsequent second allo-HCT; acute GvHD and death before acute GvHD). Time was artificially censored at 8 years after allo-HCT

TABLE 1 Characteristics of patients, disease, and transplantation by year of alloHCT

	Group	Missing N (%)	Total N (%)	2006–2008 N (%)	2009–2012 N (%)	2013–2016 N (%)
Total			904 (100.0)	264 (100.0)	394 (100.0)	246 (100.0)
Male sex			558 (61.7)	156 (59.1)	243 (61.7)	159 (64.6)
Age at allo-HCT	Median (IQR)		45.2 (35.1–54.0)	43.9 (34.3–51.9)	45.6 (35.2–54.7)	45.9 (36.7–55.0)
Year of diagnosis	Median (IQR)		2008 (2005–2011)	2005 (2004–2006)	2008 (2007–2009)	2012 (2011–2013)
Interval diagnosis - allo-HCT (months)	Median (IQR)		20.9 (11–38.4)	20.5 (11.2–36.2)	23 (12.4–42.6)	19.3 (10.2–34.7)
Number of TKI's prior allo-HCT	1		323 (35.7)	166 (62.9)	84 (21.3)	73 (29.7)
	2		371 (41.0)	86 (32.6)	191 (48.5)	94 (38.2)
	3		210 (23.2)	12 (4.5)	119 (30.2)	79 (32.1)
TKI combination received prior to allo-HCT	Only ima		247 (27.3)	156 (59.1)	59 (15.0)	32 (13.0)
	ima + dasa		229 (25.3)	63 (23.9)	128 (32.5)	38 (15.4)
	ima + nilo + dasa		176 (19.5)	12 (4.5)	113 (28.7)	51 (20.7)
	ima + nilo		99 (11.0)	23 (8.7)	51 (12.9)	25 (10.2)
	Other		153 (16.9)	10 (3.8)	43 (10.9)	100 (40.7)
Disease stage at diagnosis	CP	293 (32.4)	452 (74.0)	137 (78.3)	219 (74.5)	96 (67.6)
	AP		62 (10.1)	19 (10.9)	27 (9.2)	16 (11.3)
	BC		97 (15.9)	19 (10.9)	48 (16.3)	30 (21.1)
Disease stage at allo-HCT	CP1		549 (60.7)	174 (65.9)	225 (57.1)	150 (61.0)
	CP2		306 (33.8)	79 (29.9)	147 (37.3)	80 (32.5)
	CP3 or >		49 (5.4)	11 (4.2)	22 (5.6)	16 (6.5)
Karnofsky score	<90	175 (19.4)	120 (16.5)	25 (18.2)	54 (15.1)	41 (17.5)
	≥90		609 (83.5)	112 (81.8)	304 (84.9)	193 (82.5)
Source of graft	BM		191 (21.1)	63 (23.9)	89 (22.6)	39 (15.9)
	PB		706 (78.1)	200 (75.8)	301 (76.4)	205 (83.3)
Donor type	MRD		345 (38.2%)	129 (48.9%)	139 (35.3%)	77 (31.3%)
	MUD		353 (39.0%)	91 (34.5%)	155 (39.3%)	107 (43.5%)
	MMRD		22 (2.4%)	3 (1.1%)	9 (2.3%)	10 (4.1%)
	MMUD		146 (16.2%)	38 (14.4%)	76 (19.3%)	32 (13%)
	Unrelated[a]		38 (4.2%)	3 (1.1%)	15 (3.8%)	20 (8.1%)
Conditioning	MAC	5 (0.6)	624 (69.4)	188 (71.8)	271 (69)	165 (67.6)
	RIC		275 (30.6)	74 (28.2)	122 (31)	79 (32.4)
T-cell depleted graft	No	12(1.3)	365 (40.9)	112 (42.4)	162 (42.2)	91 (37.3)
	Yes		527 (59.1)	152 (57.6)	222 (57.8)	153 (62.7)
EBMT score	≤2		130 (14.4)	50 (18.9)	57 (14.5)	23 (9.3)
	≥3		774 (85.6)	214 (81.1)	337 (85.5)	223 (90.7)
Any Imatinib			778 (86.1)	254 (96.2)	359 (91.1)	165 (67.1)
Any Dasatinib			508 (56.2)	82 (31.1)	271 (68.8)	155 (63)
Any Nilotinib			353 (39.0)	38 (14.4)	185 (47)	130 (52.8)
Any Bosutinib			12 (1.3)		5 (1.3)	7 (2.8)
Any Ponatinib			44 (4.9)		3 (0.8)	41 (16.7)
First TKI given	Imatinib		747 (82.6)	244 (92.4)	350 (88.8)	153 (62.2)
	Dasatinib		85 (9.4)	12 (4.5)	27 (6.9)	46 (18.7)
	Nilotinib		68 (7.5)	8 (3)	17 (4.3)	43 (17.5)
	Bosutinib		1 (0.1)			1 (0.4)
	Ponatinib		3 (0.3)			3 (1.2)

TABLE 1 (Continued)

	Group	Missing N (%)	Total N (%)	2006–2008 N (%)	2009–2012 N (%)	2013–2016 N (%)
Second TKI given	Imatinib		25 (4.3)	9 (9.2)	7 (2.3)	9 (5.2)
	Dasatinib		362 (62.3)	66 (67.3)	209 (67.4)	87 (50.3)
	Nilotinib		171 (29.4)	23 (23.5)	90 (29)	58 (33.5)
	Bosutinib		8 (1.4)		4 (1.3)	4 (2.3)
	Ponatinib		15 (2.6)			15 (8.7)
Third TKI given	Imatinib		6 (2.9)	1 (8.3)	2 (1.7)	3 (3.8)
	Dasatinib		61 (29)	4 (33.3)	35 (29.4)	22 (27.8)
	Nilotinib		114 (54.3)	7 (58.3)	78 (65.5)	29 (36.7)
	Bosutinib		3 (1.4)		1 (0.8)	2 (2.5)
	Ponatinib		26 (12.4)		3 (2.5)	23 (29.1)

Abbreviations: AP, accelerated phase; BC, blast crisis; BM, bone marrow; CP1, 1st chronic phase; CP2, 2nd chronic phase; CP3, 3rd chronic phase; dasa, dasatinib; ima, imatinib; IQR, interquartile; MAC, myeloablative conditioning; MMRD, mismatched related donor; MMUD, mismatched unrelated donor; MRD, matched related donor; MUD, matched unrelated donor; nilo, nilotinib; PB, peripheral blood; RIC, reduced intensity conditioning; HCT, hematopoietic cell transplantation.
[a]Matching unknown.

for OS, PFS, RI, and NRM, at 5 years for chronic GvHD and death before chronic GvHD and at 100 days for acute GvHD and death before acute GvHD. Time to neutrophil (<1.0 $\times$ 10^9/L) and platelet (>20 $\times$ 10^9/L) engraftment were analyzed using the crude cumulative incidence estimator with death as competing event. The crude cumulative incidence estimator and Gray's test were also used to determine the cumulative incidence of any DLI (with as competing events 2nd allo-HCT and death before DLI/2nd allo-HCT).

The Cox Proportional Hazards (PH) regression model was used to investigate the role of prognostic factors and to estimate adjusted hazard ratios for OS and RFS and cause specific hazard ratios for RI, NRM, acute, and chronic GvHD. The impact of the following factors was assessed: number of TKIs prior to allo-HCT, type of TKI combination given prior to transplant (only Imatinib, Imatinib + Dasatinib, Imatinib + Nilotinib, Imatinib + Nilotinib + Dasatinib, and other combinations), disease status at transplant (CP1, CP2, or CP3), interval time between diagnosis and transplant (as a continuous linear variable and as a dichotomous variable [≤12 or > 12 months]), donor type (MRD, MUD, MMRD, and MMUD, respectively), source of cells for the transplant (PB and BM), gender mismatch (female to male and other), cytomegalovirus (CMV) status in patient and donor, T-cell depletion, conditioning intensity (MAC and RIC), age at transplant, gender and allo-HCT calendar year (2006–2010 vs. 2011–2016). The calendar year of transplantation was included in all multivariable models in an attempt to adjust for changes in clinical practice over time. Multivariable Cox PH models included only patients with complete data.

3 | RESULTS

3.1 | Patients, disease, transplant characteristics

Of a total of 3614 patients who underwent allo-HCT for CML in CP between 2006 and 2016, 904 patients (25%) from 153 centers fulfilled the inclusion criteria and were included in the study. Patient and disease characteristics, and details on pre-transplant TKI are detailed in Table 1. Transplants were performed mainly in first CP (CP1:60.7%) and mainly from MUD (39%) or MRD (38%). Median age at transplant was 45 (range [r], 18–71) years, 558 patients (61.7%) were male. The median time from diagnosis to transplant was 20.9 months (r, 1.4 months-23.3 years) and patients with three TKI prior to transplant had a longer median interval between diagnosis and transplant (14.2, 19.9, and 29.2 months for those with 1, 2, and 3 TKI, respectively, $p < .001$). Median follow-up post-transplant for the entire group was 52 months (IQR, 24–80 months). Patients who had only one TKI prior to allo-HCT had longer follow-up after transplantation (72 months, IQR 28–96 months, compared to 54 (26–77) and 37 (16–58) months for patients with two and three TKI, respectively, $p < .001$). The majority received imatinib prior to transplantation (778, 86.1%), 508 (56.2%) had received dasatinib, 353 (39.0%) had nilotinib, 12 (1.3%) had bosutinib, and 44 (4.9%) had ponatinib (Table 1). There was no significant difference regarding the cumulative incidence of donor lymphocyte infusions (DLI) given post-transplantation between patients who had one (cumulative incidence at 5 years 19% [95% CI 14–23%]), two (19% [95% CI 14–24%]), or three TKI (13% [95% CI 8–19%]) post-transplantation, $p = .31$. The same was true regarding the cumulative incidence of second transplant between patients who had one (5-year cumulative incidence 4% [95% CI 2–6%]), two (4% [95% CI 2–6%]), or three TKI (5% [95% CI 2–8%]) post-transplantation, $p = .85$. In earlier calendar years, a higher percentage of patients had received only one TKI prior to allo-HCT (63% of patients with an allo-HCT between 2006 and 2008 compared to 21% and 30% in patients with an allo-HCT between 2009–2012 and 2013–2016, respectively, $p < .001$). Patients with only one TKI prior to allo-HCT were more likely to have blast crisis (BC) at diagnosis (in 30% of patients with one TKI pre-allo-HCT compared to 11% and 4% in patients with two and three TKI's, respectively, $p < .001$). Almost all patients who received imatinib had it as first TKI prior to allo-HCT (96%). Regarding the 2GTKI, predominantly these were

utilized as second TKI prior to allo-HCT; 71.3% of patients who had dasatinib had it as second TKI and 66.7% for bosutinib. Nilotinib was used as second TKI in 48.4% of cases. As expected, the 3GTKI ponatinib was mostly given as third line (59.1%).

3.2 | Engraftment and GvHD

A total of 94.1% (851) of patients demonstrated neutrophil engraftment at a median time of 16 days (IQR, 13–20 days). Type of consecutive TKI combination pre-transplant did not impact neutrophil engraftment, ($p = .32$) and nor did the number of TKI ($p = .57$). Platelet engraftment (sustained platelet count $>20 \times 10^9$/L) occurred at a median of 15 days (IQR, 12–21 days). There was no significant impact of the type of TKI/ combinations pre-transplant did not impact platelet engraftment, ($p = .10$) and neither did the number of TKI, $p = .16$.

The 100-day cumulative incidence of aGvHD grade II-IV was 32% (95% CI 29–35%); grade III-IV was 13% (95% CI 11–15%). No significant difference existed between patients with 1, 2, or 3 TKI's prior to transplant on the incidence of aGvHD grade II-IV in univariable analyses. Day 100 incidence was 32% (95% CI 27–38%) in patients receiving one TKI, 30.0% (95% CI 25–35%) in those receiving two TKI, and 35% (95% CI 29–42%) in those receiving three TKI prior to allo-HCT, respectively, $p = .45$. Moreover, the type of TKI given prior to transplant was not significantly associated with rates of aGvHD grade II-IV; $p = .78$. In multivariable analysis, factors associated with an increased hazard of aGvHD grade II-IV included stage of disease at diagnosis, with a higher risk for patients who had AP CML relative to those with CP (Hazard ratio HR) 1.67 (95% CI 1.09–2.54%; $p = .02$), peripheral blood stem cells (PBSC) compared to BM/PBSC+BM (HR 1.73 95% CI 1.19–2.53; $p = .004$), the type of donor MUD compared to MRD: HR 2.15 (95% CI 1.51–3.07; $p < .0001$), and younger age at allo-HCT (HR per 10 years increase in age, HR 0.85 (95% CI 0.75–0.96; $p = .008$)). The cumulative incidence of all cGvHD (limited/extensive/unknown grading) at 5 years was 48% (95% CI 45–52%). Limited cGVHD accounted for 24% (95% CI 21–27%), extensive cGvHD for 19% (95% CI 16–21%), and for 6% (95% CI 4–7%) the grading was unknown. As observed for aGvHD, the number of TKI prior to transplantation was not associated with the incidence of cGvHD; the 5-year cumulative incidence was 48% (95% CI 42–54%) for patients receiving one TKI, 47% (95% CI 42–53%) for those receiving two TKI, and 49% (95% CI 42–57%) for those receiving three TKI, $p = .96$. The type of TKI combination given prior to transplant did not associate with the cumulative incidence of cGvHD, $p = .56$. In multivariable analysis, the only factor that impacted on the incidence of total cGvHD was source of stem cells, PBSC compared to BM/PBSC+BM HR = 1.42 (95% CI 1.04–1.93%; $p = .03$) and of borderline significance, the patient–donor sex combination with a higher hazard for the male recipient and female donor combination compared to other combinations, HR = 1.32 (95% CI 0.96–1.80%; $p = .09$).

3.3 | Overall survival, progression-free survival, relapse incidence, and non-relapse mortality

The 5-year OS post-allo-HCT for all patients was 64% (95% CI 61–68%) (Table 2). There was no significant association between OS and the number of TKI given prior to allo-HCT (Table 2 and Figure 1A), $p = .34$ or the type of TKI combination given prior to allo-HCT (Table 2), $p = .71$.

This was confirmed in multivariable analysis, here, the only factors that were significantly associated with a worse OS were being in CP2 or CP3 as compared to CP1 and a lower Karnofsky score (Table 3). We found no evidence that the association between the number of TKI given and OS differed in patients being in CP1 and CP2 or CP3 (test for interaction $p = .85$) or according to the type of TKI combination ($p = .89$). Of the patients who died, 24% died due to relapse, 34% due to GvHD, 24% due to infection, and 18% due to other causes, with no significant difference in the distribution of causes of death between patients who received 1, 2, or 3 TKI prior to allo-HCT, $p = .89$.

The 5-year PFS post-allo-HCT for all patients was 48% (95% CI 44–51%) (Table 2). There was no significant association between the number of TKI's given prior to transplant and PFS in univariable analyses (Table 2 and Figure 1B), and neither was the type of combination of TKI given (Table 2), $p = .2$. Number of TKI's prior to allo-HCT and type of TKI combination received were not significantly associated with either OS or PFS in the multivariable analysis. As observed for OS, the only factors that were associated with a worse PFS were CP2 or CP3 (compared to CP 1) and a lower Karnofsky score (Table 3). No significant interaction between disease stage at allo-HCT and either the number of TKI ($p = .23$) or the type of TKI combination was observed ($p = .37$).

The 5-year cumulative incidence of relapse (RI) post-allo-HCT for all patients was 29% (95% CI 26–32%) (Table 2). No impact on RI was observed from either the number of TKI given prior to transplant ($p = .13$, Table 2 and Figure 1C) or type of TKI combination given ($p = .18$, Table 2). In the multivariable analysis, there was a trend for a higher cause specific hazard for relapse in patients who had two (HR 1.49, 95% CI 1.04–2.14, $p = .03$) or three TKI (HR 1.54, 95% CI 0.99–2.39, $p = .05$) compared to patients receiving only one TKI. Additionally, factors that were significantly associated with a higher cause specific hazard of relapse were being in CP2 or CP3 phase of the disease prior to allo-HCT, a lower Karnofsky score and a shorter interval between diagnosis and allo-HCT (Table 3).

The 5-year cumulative incidence of non-relapse mortality (NRM) post-allo-HCT for all patients was 23% (95% CI 20–26%) (Table 2). There was no significant association between NRM and the number of TKI given prior to transplant ($p = .94$, Table 2 and Figure 1D) or the type of combination of TKI given ($p = .98$, Table 2). Moreover, we did not observe a significant association between NRM and number or type of TKI and any of the other factors in multivariable models (Table 3).

TABLE 2 Outcome at 5 years after alloHCT of patients receiving 1, 2, or 3 TKI's and type of TKI combination prior to alloHCT

All patients	5-y OS (95% CI) 64% (61–68%)	5-y PFS (95% CI) 48% (44–51%)	5-y RI (95% CI) 29% (26–32%)	5-y NRM (95% CI) 23% (20–26%)
Number of TKI's prior to alloHCT				
1	66% (60–72%)	50% (44–57%)	26% (21–32%)	23% (18–28%)
2	62% (56–67%)	44% (39–50%)	33% (28–38%)	23% (18–27%)
3	68% (60–75%)	51% (42–60%)	25% (19–32%)	24% (16–31%)
p-value*	.34	.12	.13	.94
Type of TKI combination				
Only imatinib	67% (60–73%)	51% (44–58%)	26% (20–32%)	23% (17–29%)
Imatinib + dasatinib	63% (56–70%)	43% (36–49%)	35% (28–42%)	23% (17–28%)
Imatinib + nilotinib + dasatinib	68% (60–76%)	52% (43–62%)	23% (17–30%)	24% (16–33%)
Imatinib + nilotinib	61% (50–72%)	48% (36–59%)	29% (19–39%)	23% (14–33%)
Other	61% (51–71%)	47% (36–58%)	29% (21–36%)	25% (15–35%)
p-value*	.71	.20	.18	.98

Abbreviations: CI, confidence interval; NRM, non-relapse mortality; OS, overall survival; PFS, progression-free survival; RI, relapse incidence; TKI, tyrosine kinase inhibitor.

**p*-values were obtained with the log-rank test (OS and PFS) and Gray's test (RI and NRM) with time artificially censored at 5 years.

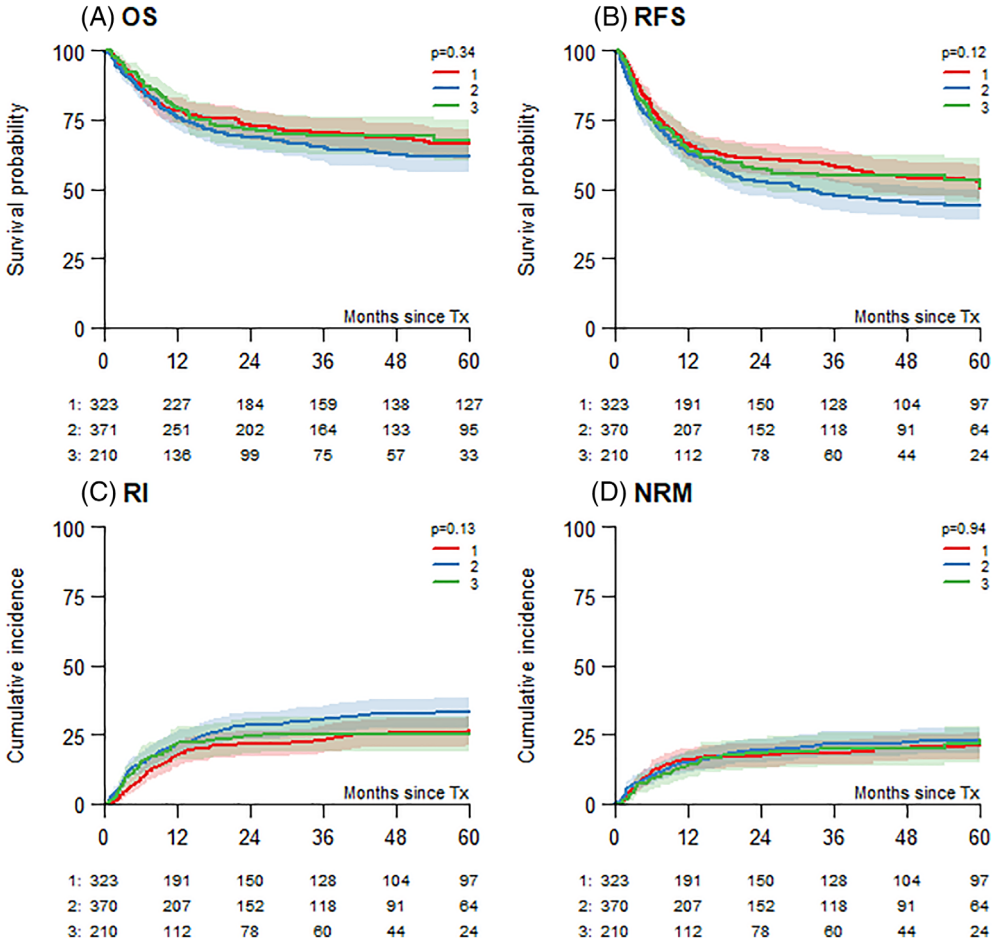

FIGURE 1 Overall survival (OS), relapse free survival (RFS), relapse incidence (RI) and non-relapse mortality (NRM) of CML patients who had 1, 2 or 3 TKI's prior to allo-HCT. Numbers below the graph show the number of patients at risk [Color figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

This study describes outcomes in CML patients undergoing allo-HCT between 2006 and 2016 who were treated with different TKI prior to transplantation. During this period, the second and third generation TKI were progressively introduced into standard clinical care. As demonstrated by previous studies where imatinib was given as the only TKI prior to transplant,[15,16] we find in this study similar engraftment

TABLE 3 Multivariable analysis for OS, PFS, RI, and NRM using Cox proportional (cause specific) hazards models. For RI and NRM cause specific hazard ratios were obtained

		OS HR (95% CI)	*p*	PFS HR (95% CI)	*p*	RI HR (95% CI)	*p*	NRM HR (95% CI)	*p*
Age at alloHCT	per 10 year increase	1.06 (0.95–1.20)	.31	1.03 (0.94–1.14)	.52	1.02 (0.90–1.17)	.73	1.04 (0.90–1.21)	.60
Number of TKI's prior alloHCT	1	1.00		1.00		1.00		1.00	
	2	1.15 (0.84–1.58)	.37	1.28 (0.98–1.67)	.07	1.49 (1.04–2.14)	.03	1.05 (0.71–1.57)	.80
	3	1.07 (0.73–1.56)	.74	1.20 (0.87–1.66)	.27	1.54 (0.99–2.39)	.05	0.88 (0.54–1.41)	.58
Year of alloHCT	2006–2010	1.00		1.00		1.00		1.00	
	2011–2016	1.13 (0.86–1.48)	.37	1.01 (0.81–1.27)	.92	0.85 (0.63–1.15)	.29	1.27 (0.90–1.78)	.18
Stage of disease at alloHCT	CP1	1.00		1.00		1.00		1.00	
	CP2 or CP3	1.50 (1.14–1.97)	.004	1.44 (1.14–1.82)	.002	1.73 (1.26–2.38)	.0007	1.15 (0.81–1.62)	.44
Interval diagnosis – alloHCT	<1 year	1.00		1.00		1.00		1.00	
	≥ 1 year	0.85 (0.61–1.18)	.32	0.81 (0.61–1.06)	.13	0.59 (0.42–0.84)	.004	1.27 (0.80–1.99)	.31
Karnofsky score	80 or lower	1.00		1.00		1.00		1.00	
	90 or 100	0.55 (0.41–0.75)	.0001	0.66 (0.51–0.87)	.003	0.58 (0.41–0.82)	.002	0.78 (0.51–1.20)	.25
EBMT risk score	3	1.00		1.00		1.00		1.00	
	1 or 2	1.05 (0.63–1.75)	.85	1.02 (0.67–1.55)	.92	0.92 (0.54–1.56)	.75	1.21 (0.612.42)	.59
Donor/patient sex match	Other	1.00		1.00		1.00		1.00	
	F- > M	1.34 (0.99–1.83)	.06	1.09 (0.83–1.43)	.56	0.84 (0.57–1.24)	.38	1.43 (0.98–2.10)	.07

Abbreviations: allo-HCT, allogeneic hematopoietic cell transplantation; CI, confidence interval; CP1, 1st chronic phase; CP2, 2nd chronic phase; CP3, 3rd chronic phase; F, female; HR, hazard ratio; M, male; NRM, non-relapse mortality; OS, overall survival; PFS, progression free survival; RI, relapse incidence; TKI, tyrosine kinase inhibitor.

rates and acute/chronic GvHD incidence despite the use of TKI prior to transplant. Moreover, no difference regarding those outcomes was apparent whether the patient received 1, 2, or 3 TKI prior to allo-HCT, except for relapse where there was a tendency toward higher relapse post-transplant for those who had 2 or 3 TKI as compared to 1 TKI (Table 3). Similarly, the choice of TKI given did not impact on these outcomes.

With the advent of TKI in the early 2000s, there has been a yearly decrease of the number of allo-HCT for CML globally, as shown for example by the number of allo-HCT reported to the EBMT registry which decreased from 561 in 2006 to 329 in 2016. Importantly, it is not only the number of transplants for CML that has decreased, but also that the phase of disease at transplant differs. More patients are being transplanted in advanced phases, for example, BC accounted for 10% of transplants in 2007 and 21% in 2016. In keeping with this, there was decrease in CP1 transplants over this period from 50% to 42%. In our study, we see an increase in the number of TKI used prior to allo-HCT over time in keeping with changes in CML practice; one TKI at a median year of 2008 to three TKI at a median year of 2012. This reflects the major changes in practice related to the successive introduction of 2GTKI like nilotinib, dasatinib, and bosutinib and 3GTKI such as ponatinib that allowed patients who are intolerant or resistant to first generation TKI to switch to alternative TKI prior to taking the decision to go to allo-HCT. Also of note, the percentage of patients undergoing allo-HCT being in BC at diagnosis was higher in those receiving only one TKI (30%) compared to those receiving two TKI (11.1%) and three TKI (4.4%). This likely reflects the fact that eligible BC patients, if put into CP, went rapidly to allo-HCT and therefore did not receive many lines of TKI prior to transplantation.

Of note in the present study, imatinib was still used in the vast majority of allo-HCT CML patients in first line (82%), even though currently 2GTKI are proposed more often as first line therapy, although still debatable,[7,17] but particularly for high or intermediate risk Sokal score patients. This is probably explained by the fact that 2GTKI were not immediately available as first line therapy in many countries, and that approval for use in the first line setting has been more recently adopted. Dasatinib was the 2GTKI that was most frequently used as first line among 2GTKI and 3GTKI and additionally the most commonly used in second line, representing 62% of the 2TKI given. As expected, the 3GTKI ponatinib, the most recently approved gent, proportionally was used in preference as third TKI (Table 1; representing 59.1% of use of ponatinib in total), but in absolute number it was nilotinib that was mostly used as third line TKI, representing 114/210 (54%) patients who received a third TKI prior to transplantation.

The general outcome of the CML patients transplanted in CP in this study with a 5-year OS of 64%, PFS of 48%, RI of 29.7%, and NRM of 23% appears worse compared to studies in patients transplanted in CP and with a good EBMT risk score (0–2), those who had imatinib failure and underwent allo-HCT,[18–20] or those undergoing RIC conditioning combined with imatinib pre- and post-transplant.[21,22] This can be explained by the fact that in the present analysis there was a mix of low and high-risk patients, with 40% of the cohort at transplant being in CP2 or CP3, paralleled by an increase over time of the percentage of patients transplanted in more advanced phase (see above). Multivariable analysis demonstrated that patients in CP2 or CP3 had worse outcomes when compared to patients transplanted in CP1. These results, in addition to those from other studies,[20,23] highlight that, despite great progress with the advent of new generations of TKI allowing CML-treating physicians to consecutively propose another therapeutic option, when considering allo-HCT as a rescue therapy, this should be done in CP1 to optimize success, and less NRM and RI than if the patients have already progressed to either AP or BC and undergoing treatment to CP2 or higher. This is in line with the recently updated indications for allo-HCT for CML from the EBMT published online.[24] It is therefore very important to closely monitor patients with BCR-ABL evaluation every 3 months and when the kinetic of the BCR-ABL/ABL ratio is increasing over major molecular response constantly on at least two successive occasions (0.1% international scale), discuss rapidly the different options, and particularly allo-HCT if the patient has already received three different TKI, and most certainly if ponatinb was one of the TKI given. The same holds true for patients being intolerant due to cytopenia and who cannot be treated accordingly with optimal dose density which precludes maximal therapeutic responses and puts them at risk of evolving to advanced stage CML. One issue is the lack of robust prognostic factors determining which patients will be at risk of suboptimal/absent response to second or third line TKI, which could aid decision making alongside BCR-ABL evaluation and possibly help avoid disease progression to advanced phase prior to consideration to allo-HCT although the ELN 2020 criteria could help with their definition of optimal and failure responses to second line TKI therapy.[25]

As opposed to a previous study demonstrating worse outcomes in those patients receiving three or more TKI's prior to allo-HCT compared to those with less than three TKI's,[26] we did not find any impact on OS, PFS, or NRM as determined by the number of TKI given prior to transplantation. We demonstrate an impact on relapse incidence which was higher for patients receiving two or three TKI prior to transplantation. This difference between both studies may be related to the differing populations undergoing evaluation, one with Japanese patients and one with a population with a European background. This may also be in relation to the different periods studied; Kondo et al. analyzed patients transplanted between 2001 and 2012 whereas our analysis spanned between 2006 and 2016. This may indeed influence outcomes due to possible improvements in supportive care during transplantation over the years. Of note, the differences in outcome observed in that study were mostly related to increased NRM, whereas in our study NRM was not affected by the number of TKI given prior to allo-HCT. In addition, these differences may also be related to the different proportion and use of TKI in the previous study when the use of 2GTKI and even 3GTKI was less prevalent. The type of TKI given prior to allo-HCT was not significantly associated with either OS, PFS, RI, or NRM in this study.

About 21% of the cohort also received TKI post-transplantation. The most frequent TKI used post allo-HCT was dasatinib (42%) followed, interestingly, by imatinib (24%) demonstrating that although most of the patients had received imatinib prior to alloHSCT, this TKI

was still quite frequently used post-transplant. However, robust inferences on this aspect cannot be made as there is a lack of data regarding the reason to give the TKI after allo-HCT. Nonetheless, one may speculate that imatinib was still preferred post-transplant in a substantial number of patients because of better tolerance or longer clinical experience with this TKI as opposed to 2GTKI and 3GTKI.

We would also like to stress that there are limitations in this study mainly due to its retrospective nature and long observation period. Moreover, the study cohort of 904 patients evaluated with sufficient data represents only 40% of the 2246 patients in the EBMT database who were transplanted for CML in CP between 2006 and 2016.In addition, as the study period ended over 5 years ago, this may not reflect contemporary strategies for allo-HCT in CML patients. Nonetheless, it is our belief that this study highlights new and important insights in the outcome of a large group of CML patients post allo-HCT in the TKI aera.

In summary, results of the present study suggest that the number of TKI nor the choice of TKI given prior to allo-HCT for CML impacts upon survival outcome of those patients, which also reflects that the biology of the disease most likely determines the overall outcome.

This is reassuring for CML patients in need of allo-HCT nowadays as most will have received at least two TKI. The phase of the disease at transplant remains a major factor influencing outcomes and the results presented here highlight the fact that CML patients should be maintained as much as possible in CP1 before proceeding to transplantation. CML-treating physicians should monitor patients closely as per current ELN guidelines to avoid progression to advanced phase and a need of salvage therapy to put them back into CP2 or CP3, as transplantation outcomes will clearly be below what can be achieved for those patients remaining in CP1. Lastly, performance status at time of allo-HCT remains an important predictive factor in the era of third generation TKI.

AUTHOR CONTRIBUTIONS

YC and NK designed the study. LK, JA, JB, US, HS, MA, GH, CC, GC, PR, JS, RPdL, SL, SM, JP, AECB, ZNO, SMT, PJH, IY-A, DPM, NK contributed to the data and reviewed the manuscript. YC, GS, and LG analyzed the data. YC, GS, LG, LK, DPM, IY-A, NK wrote the manuscript.

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DATA AVAILABILITY STATEMENT

Data are available through the EBMT data center in Leiden e-mail: CMWPebmt@lumc.nl.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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