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Tyrosine kinase inhibitor-related factors pre-disposing to post-transplant thrombotic microangiopathy in patients with CML and Ph+ acute leukemias

Sachin Punatar[1,2], Komal Kumbhalwar[1], Siddhesh A Kalantri[1,2], Anant Gokarn[1,2], Lingaraj Nayak[1,2], Akanksha Chichra[1,2], Sumeet Mirgh[1,2], Nishant Jindal[1,2], Libin Mathew[1], Sadhana Kannan[3], Navin Khattry[1,2]

[1]HSCT unit, Department of Medical Oncology/Advanced Centre For Treatment Research & Education in Cancer, Tata Memorial Centre, Navi Mumbai, India, [2]Homi Bhabha National Institute, Mumbai, India, [3]Department of Biostatistics/ Paymaster Shodhika/Advanced Centre For Treatment Research & Education in Canter, Tata Memorial Centre, Navi Mumbai, India

Abstract

Introduction: We have previously reported that pre-transplant use of tyrosine kinase inhibitors (TKIs) is independently associated with the occurrence of transplant-associated thrombotic microangiopathy (TA-TMA). However, the precise TKI-related factors which predispose to TA-TMA are unknown. In this retrospective analysis, we identify the TKI-related factors that are associated with TA-TMA.

Methods: This was a single center retrospective analysis of all patients with Philadelphia chromosome-positive (Ph+) malignancies who received BCR-ABL TKIs prior to transplant and underwent allogeneic hematopoietic stem cell transplantation (HSCT) between January 2008 and March 2019. Definite TA-TMA was defined as per Blood & Marrow Transplant Clinical Trials Network (BMT CTN) criteria and probable TMA as per Cho criteria. Details about the timing of the start and stop of TKI pre-transplant, the dose of TKIs used, and the number of TKIs exposed to pre-transplant were obtained. Imatinib > 400 mg/day, dasatinib > 100 mg/day, or nilotinib > 800 mg/day were considered as high dose TKI.

Results: Seventy-two patients with chronic myeloid leukemia (CML)/Ph+ acute leukemias underwent transplant in the above period. Patient, donor, and transplant characteristics are shown in Table 1 and were well-matched between those with and without TMA. Overall, 13 (18%) had TA-TMA (median day +128), with 9 definite and 4 probable. The only TKI-related factor significantly associated with TA-TMA was the use of high-dose TKI (p= 0.04). Among non-TKI-related factors, acute graft versus host disease (GVHD) was associated with TA-TMA (p= 0.01). On multivariate analysis, high dose TKI did not remain statistically significant (Odds Ratio (OR) 4.6, p= 0.16). TA-TMA was associated with significantly worse long-term survival (6-year survival was 30% with TMA versus 62% without TMA, p=0.026).

Conclusions: Pre-transplant use of TKI was associated with risk of TMA in about one-fifth of patients. High-dose TKI and acute GVHD increased the risk of TA-TMA. Prospective studies are warranted to confirm these findings. TA-TMA was associated with significantly worse long-term survival.

Key words tyrosine kinase inhibitor, transplant associated thrombotic microangiopathy, chronic myeloid leukemia, Philadelphia positive acute leukemias

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Correspondence: Navin Khattry, HSCT unit, Department of Medical Oncology, Room no 211,Paymaster Shodhika, ACTREC, Tata Memorial Centre Kharghar, Navi Mumbai 410210, Maharashtra, India, E-mail: nkhattry@gmail.com

Introduction

Allogeneic hematopoietic stem cell transplant (allo-HSCT) is the only curative option for a number of hematological malignant and benign disorders as well as several inherited disorders. However, the success of allo-HSCT is hampered by the occurrence of acute and chronic post-transplant complications which often lead to transplant-related mortality (TRM). The important acute complications leading to TRM include acute graft

versus host disease (GVHD), infections, and transplant-associated thrombotic microangiopathy (TA-TMA)[1-4].

TA-TMA is a major complication post allo-HSCT. Research on the risk factors and implications of TA-TMA was marred by the lack of a uniform definition of TA-TMA for several decades. However, the Blood & Marrow Transplant Clinical Trials Network (BMT CTN)[5] and Cho criteria[6] have made the diagnosis more uniform, which has helped further the identification of risk factors for TA-TMA. These criteria have subsequently been revised. Harmonized criteria for diagnosis and prognostic assessment of TA-TMA have recently been published[7]. While several studies have shown acute GVHD, myeloablative conditioning, and alternate donor transplants as being associated with the occurrence of TA-TMA, the other risk factors are somewhat controversial with different studies showing conflicting results[3, 8, 9]. We have previously reported that use of tyrosine kinase inhibitors (TKIs) prior to allo-HSCT independently and significantly increases the risk of post-transplant TMA[10]. However, which precise factor related to TKI use pre-transplant leads to this risk was not addressed in that study. We conducted this retrospective analysis in order to identify precise TKI-related factors which contribute to the risk of TA-TMA.

Materials and Methods

This was a retrospective single center analysis of all patients with either chronic myeloid leukemia (CML) or Philadelphia chromosome-positive (Ph+) acute leukemias who underwent allo-HSCT between January 2008 and March 2019. The study was approved by the institutional ethics committee (IEC-III of Tata Memorial Centre, protocol number 900863). Given the nature of the study, the need for consent was waived by the ethics committee.

All patients had received one or more BCR-ABL TKIs prior to transplant. Details of conditioning regimen, transplant procedures, and GVHD prophylaxis have been published previously[10]. While all patients had received pre-transplant TKI, no patient received prophylactic TKI. Post-transplant TKIs were started only in the event of molecular or cytogenetic relapse (for CMLs), detection of minimal residual disease (for acute leukemias), overt hematological relapse (for both CMLs and acute leukemias), or for slippage of chimerism (for both CMLs and acute leukemias). TA-TMA was defined as per the BMT CNT criteria for definite TMA[5] and Cho criteria[6] for probable TMA. Although the harmonized criteria for diagnosis of TA-TMA have now been published[7], we did not utilize them as sC5b-9 levels and spot urine protein creatinine ratio were not available for the patients. Patients with a diagnosis of TMA were managed with supportive measures and stoppage of calcineurin inhibitors whenever feasible. Some patients received defibrotide. No patient was treated with eculizumab or narsoplimab. No patient received any form of experimental therapy for TMA.

We evaluated 5 TKI-related factors as potential risk factors for TMA - the total duration of TKI use pre-transplant, the number of TKIs used, the TKI washout period given prior to HSCT, the use of high-dose TKI, and the last TKI used prior to HSCT. The total duration of TKI used pre-transplant was calculated from the date (or month) of the initial start of TKI and its stop date before transplant. The washout period before transplant was calculated as the number of days from the last day of TKI use to day 0 (day of infusion). The highest dose of TKI received was also noted and any dose higher than the standard dose of TKI (as used in CML) was considered as high dose TKI. Therefore, high dose TKI was defined as imatinib > 400 mg/day, dasatinib > 100 mg/day, or nilotinib > 800 mg/day. Additional (non-TKI-related) risk factors assessed were acute GVHD and haplo-identical transplants (since these were other independent risk factors in our previous analysis[10] as well as in many other studies). GVHD was treated as a time-dependent variable. It was taken as a risk factor for TMA only when the onset of GVHD was before onset of TMA. The grading and staging of GVHD was as per the modified Glucksberg criteria. Univariate analysis for these risk factors was done using a chi-square test and Mann Whitney test as appropriate. Risk factors identified as significant (i.e. with a p value < 0.05) on univariate analysis were subject to multivariate analysis using logistic regression. Overall survival was calculated from day 0 and was compared between patients with and without TMA using the Kaplan-Meier method. All statistical analysis was performed using SPSS software.

Results

Seventy-two patients with Ph+ acute leukemias or CML underwent allo-HSCT in the above period. The baseline patient, donor, and transplant characteristics are shown in **Table 1**. None of the patients had a prior (pre-HSCT) TKI-related vascular complication. Overall, 13 patients (18%) developed TMA in this cohort. Nine of these were definite TMA, and 4 were probable TMA, as per the BMT CTN and Cho criteria. Amongst all 13 patients, the median day of diagnosis of TMA post-HSCT was day +128. For analysis, patients were divided into those with TMA (n=13) and those without TMA (n=59). There were no significant differences between the baseline characteristics of these two groups of patients (**Table 1**).

Table 1. Baseline characteristics

Characteristic	Whole cohort (n=72)	TMA group (n=13)	No TMA (n=59)	*p* value
Patient age				0.79
Median, range	28.5 (12 – 55)	29 (13 – 51)	28 (12 – 55)	
Patient gender				0.49
Males	53	11	42	
Females	19	2	17	
Donor age				0.06
Median, range	30.5 (6 – 57)	29 (17 – 47)	33 (6 – 57)	
Donor gender				0.75
Males	47	8	39	
Females	25	5	20	
Diagnosis				0.59
CML	52	9	43	
Ph positive ALL	17	4	13	
Ph positive AML	3	0	3	
Disease status at diagnosis For CML only				0.82
Chronic phase	39	8	31	
Accelerated phase	7	1	6	
Blast crisis	6	0	6	
Disease status at transplant For CML only				0.99
Chronic phase	50	9	41	
Accelerated phase	0	0	0	
Blast crisis	2	0	2	
Blast crisis before transplant For CML only				0.70
Yes	16	2	14	
No	36	7	29	
Disease status at HSCT For acute leukemias only				0.99
CR1	18	4	14	
CR2 or beyond	2	0	2	
Not in CR	0	0	0	
Pre-HSCT TKI related vascular/thrombotic events				1.00
Yes	0	0	0	
No	70	13	57	
Missing data	2	0	2	
Type of transplant				0.54
Matched related donor	53	9	44	
Matched unrelated donor	3	0	3	
Haplo-identical donor	16	4	12	
Source of stem cells				1.00
PBSC	70	13	57	
BM	2	0	2	
Conditioning regimen				0.72
Full intensity	16	2	14	
Reduced intensity	56	11	45	
CD34 cell dose infused*, median	4.9	4.7	4.9	0.65
CD3 cell dose infused*, median	123.0	119.3	123.4	0.36
GVHD prophylaxis				0.72
CNI + MTX/MMF	54	9	45	
CNI + MMF + PTCy	17	4	13	
Other	1	0	1	

* Both CD34 and CD3 cell doses are expressed in 10^6/kg. For CD3, n=71 for the whole cohort, and 58 for the no TMA group (not available for 1 patient)

TMA, Thrombotic microangiopathy; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; AML, acute myeloid leukemia; HSCT, hematopoietic stem cell transplant; CR, complete response; TKI, tyrosine kinase inhibitor; PBSC, peripheral blood stem cells; BM, bone marrow; GVHD, Graft versus host disease; CNI, Calcineurin inhibitor; MTX, Methotrexate; MMF, Mycophenolate Mofetil; PTCy, Post transplant cyclophosphamide

Table 2. Univariate analysis of TKI related risk factors

Characteristic	Whole cohort (n=72)	TMA group (n=13)	No TMA (n=59)	*p* value
Number of pre-HSCT TKI, median	2	2	2	0.38
Cumulative duration of TKI use pre-HSCT, median (months)	21.6	30.9	20.3	0.63
Pre-HSCT washout period in days, median (n=47)	19	13 (n=7)	21.5 (n=40)	0.92
Use of high dose TKI, n (%)				0.04
Yes	46	12	34	
No	21	1	20	
Missing data	5	0	5	
Last TKI pre-HSCT, n (%)				0.93
Imatinib	31	6	25	
Nilotinib	10	2	8	
Dasatinib	31	5	26	

HSCT, hematopoietic stem cell transplant; TKI, tyrosine kinase inhibitor; TMA, thrombotic microangiopathy

Table 3. Univariate analysis of non-TKI related risk factors

Characteristic	Whole cohort (n=72)	TMA group (n=13)	No TMA (n=59)	*p* value
Type of transplant				0.47
Haplo-identical transplants	16	4	12	
Others	56	9	47	
Acute GVHD				0.01
Yes	36	11	25	
No	36	2	34	

GVHD, graft versus host disease; TMA, thrombotic microangiopathy

Table 4. Multivariate analysis of risk factors for TMA

Factor		Odds ratio with 95% CI	*p* value
Acute GVHD	No	Reference	0.016
	Yes	8.34 (1.4 – 46.9)	
High dose TKI	No	Reference	0.16
	Yes	4.69 (0.5 – 41.0)	

GVHD, graft versus host disease; TKI, tyrosine kinase inhibitor; CI, confidence interval; TMA, thrombotic microangiopathy

Univariate analysis of TKI-related risk factors

The median number of TKIs used prior to transplant were 2 in both groups. Although the median cumulative duration of TKI use pre-transplant was longer by nearly 11 months amongst patients who developed TMA, this was not statistically significant. Data on the exact washout time prior to transplant was available for 47 patients. The median TKI washout time given prior to stem cell infusion was lesser by nearly 9 days amongst those with TMA, but this difference was also not statistically significant. Data about the use of high-dose TKI was available for 67 patients. Amongst them, 46 had received high dose TKI and 21 had not. Twelve out of 46 patients who had received high dose TKI developed TMA (26%) compared to only 1 of 21 (4.7%) without exposure to high dose TKI, and this difference was statistically significant (p=0.04). The last TKI used prior to transplant was not different in the two groups. These findings are summarized in **Table 2**.

Univariate analysis of non-TKI-related risk factors

Amongst the non-TKI-related risk factors, only acute GVHD was a significant risk factor (**Table 3**). Amongst patients who had GVHD and TA-TMA, the median time to develop TMA was 28 days after GVHD (range 3 to 65 days). Although patients with haplo-identical transplants had increased TMA compared to the others (25% versus 16%), this difference was not statistically significant.

Multivariate analysis

Two factors were included in multivariate analysis - use of high dose TKI prior to transplant and acute GVHD. Logistic regression (**Table 4**) identified acute GVHD to be associated with a nearly eight-fold increased risk of TMA (p=0.016). High dose TKI was associated with a nearly four-fold increased risk of TMA although this did not remain significant on multivariate analysis (p=0.16).

Impact of high dose TKI on GVHD and TRM

The proportion of patients developing acute GVHD was not significantly higher in the high dose TKI group (**Table 5**). Similarly, the proportion of patients with

TRM was also not higher in the high dose TKI group (**Table 5**).

Impact of TA-TMA on survival

TA-TMA was associated with a significantly worse overall survival with the 6-year survival being 30% in those with TMA compared to 62% in those without. The median overall survival was 1.1 years in those with TA-TMA versus not reached in those without (p=0.026, **Figure 1**).

Discussion

TA-TMA is a severe post-transplant complication and is associated with a significantly poor prognosis. In spite of this being known for nearly three decades, the risk factors for TMA have not been very clearly defined. While several risk factors have been proposed, two factors which have consistently been shown to be associated with TMA across many studies are acute GVHD and haplo-identical transplants. Calcineurin inhibitors have also been shown to be a significant risk factor for the occurrence of TA-TMA. However, results of studies addressing other risk factors like bacterial or viral infections, patient gender, intensity of conditioning regimen, etc., have been inconsistent and often conflicting[3, 8, 9].

Vascular complications with various TKIs have been well known for the last 10 years or more and have been the focus of several reviews and meta-analyses[11-13]. TA-TMA being an endothelial complication was very likely to be impacted or influenced by TKIs. We have previously shown that pre-transplant use of TKIs was a strong and independent risk factor for TA-TMA[10]. In our previous study, patients who had received TKI prior to transplant had a nearly three-fold increased risk of development of TMA which was statistically significant and remained an independent risk factor on multivariate analysis. However, the precise TKI-related risk factors were not addressed in our previous study.

In our study, patients with TMA had received a longer duration of TKIs by nearly 10 months and also had a shorter median washout period by 8 days. Both of these differences were not statistically significant, possibly because of the low numbers of patients with TA-TMA. However, we did identify that the use of higher doses of TKI before transplant is associated with increased risk of TMA. These findings are in line with studies correlating dose and duration of TKIs with vas-

Table 5. Impact of high dose TKI on transplant outcomes (n=67)

Outcome	High dose TKI group (n=46)	No high dose TKI group (n=21)	p value
Acute GVHD	26	8	0.19
TA-TMA	12	1	0.04
TRM	14	5	0.57

GVHD, graft versus host disease; TA-TMA, transplant associated thrombotic microangiopathy; TRM, transplant related mortality; TKI, tyrosine kinase inhibitor

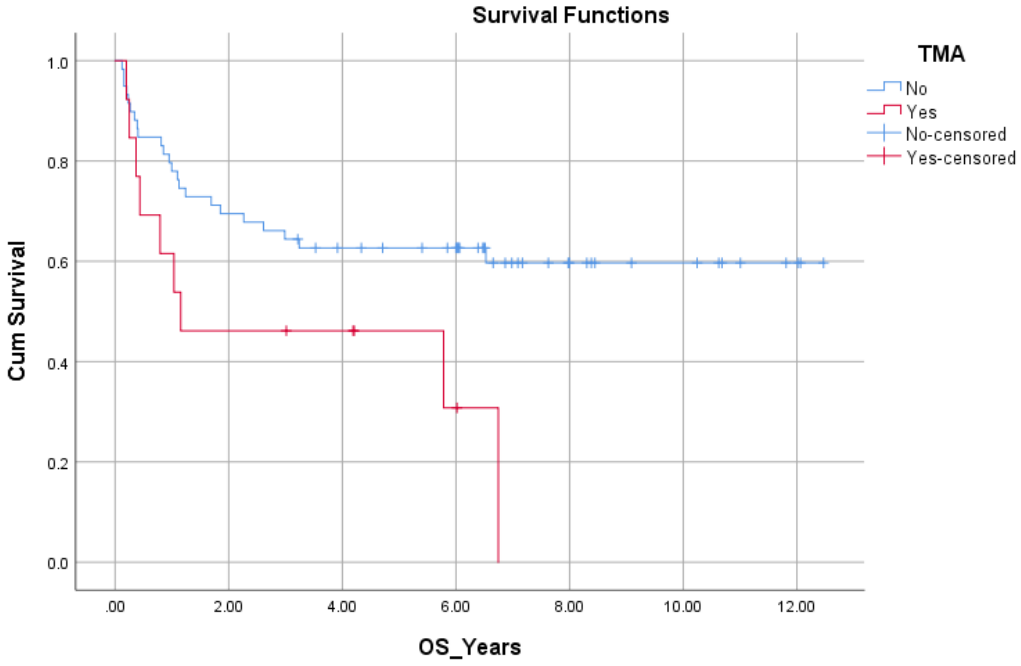

Figure 1. Overall survival of patients with TMA (red line) versus those without TMA (blue line).
The X-axis is time in years and the Y-axis is the proportion of patients alive. The vertical bars indicate censored data

cular complications. Several studies have shown that vascular complications increase with a longer duration of TKIs and that higher doses of TKIs are associated with more vascular complications[11, 14-17]. As hypothesized in our previous study, the increased risk of TMA is likely because of the vascular effects of the TKIs. Therefore, it seems logical that high doses of TKI would be associated with an increased risk of TMA, as they would likely lead to more vascular effects. Although multivariate analysis did not confirm the effect of the TKI dose, this is likely due to the small number of events.

Although this study has the limitations of being a retrospective study and the findings do need to be confirmed in prospective studies, there are likely certain clinical implications of the findings of this study. For example, for patients with CML failing imatinib 400 mg/day, using a second-generation TKI (like dasatinib) may be considered rather than increasing the dose of imatinib to 600 mg/day. Also, in patients with Ph+ acute lymphoblastic leukemia (ALL), the standard dose of imatinib is 600-800 mg/day and dasatinib is 140 mg/day based on data from several clinical trials[18-20]. Given that transplant is the only curative treatment for adults for Ph+ ALL, these recommendations need to relooked into, especially in the face of clinical studies showing similar results with lower doses of TKIs[21]. Lower doses of dasatinib have also been shown to be effective in CML[22-23].

In conclusion, this study has provided a potential lead in identifying that high doses of TKI pre-transplant may increase the risk of TA-TMA. The findings of this study need to be confirmed in larger and/or prospective studies. These findings are likely to have clinical implications in the management of patients with CML and Ph+ acute leukemias.

Author Contributions

SP, SAK, and NK designed the study. SP, KK, SK, AG, LN, AC, SM, NJ, and LM collected the data. SK performed the data analysis. SP wrote the first draft of the manuscript. All authors reviewed and revised the manuscript.

Conflicts of Interest

The authors declare no conflict of interest. Disclosure forms provided by the authors are available on the website. NK is one of the editors of Blood Cell Therapy. He was not involved in the editorial evaluation or decision to accept this article for publication.

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