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Research paper

The management and outcomes of patients with myelodysplastic syndrome with persistent severe thrombocytopenia: An observational single centre registry study

Abi Vijenthira[a], Devyani Premkumar[b], Jeannie Callum[c,d], Yulia Lin[c,d], Richard A. Wells[e,f], Lisa Chodirker[e,f], Martha Lenis[e], Alexandre Mamedov[e], Rena Buckstein[e,f,*]

[a] Postgraduate Medical Education, University of Toronto, Toronto, ON, Canada
[b] Sunnybrook Health Sciences Centre, Toronto, ON, Canada
[c] Department of Laboratory Medicine and Molecular Diagnostics, Sunnybrook Health Sciences Centre, Canada
[d] Department of Laboratory Medicine and Pathobiology, University of Toronto, Toronto ON, Canada
[e] Department of Hematology/Oncology, Odette Cancer Center, Sunnybrook Health Sciences Centre, Canada
[f] Department of Medicine, University of Toronto, Toronto, ON, Canada

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ABSTRACT

Background: Severe thrombocytopenia affects 10% of patients with myelodysplastic syndrome (MDS) and is associated with poor outcomes. The role for prophylactic platelet transfusions in the outpatient setting is unknown.

Objective/methods: To audit treatments, bleeding rates, and transfusion requirements of patients with MDS and persistent severe thrombocytopenia (PST) registered in a prospective MDS registry at our center.

Results: 99 (17%) of 586 total registry patients had PST; 28 were treated with tranexamic acid alone (TXA), 39 with TXA and prophylactic platelet transfusions (PROPH), 19 with PROPH alone, and 13 were untreated. Median duration of PST was 27 weeks and median overall survival was 0.9 years (95% CI 0.7–1.2). During the PST, 6% (6/99) of patients had a grade 4 bleeding event, from which 4 died. Platelet count at the time of grade 4 bleeding ranged from 2 to 19 $\times 10^9$/L. 66% (27/41) of patients on TXA alone or untreated required no therapeutic platelet transfusions and experienced no grade 3–4 bleeds. There were no significant differences in grade 3–4 bleeding rates between groups.

Conclusions: Patients with MDS and PST had low rates of major bleeding but poor overall survival. Disparities in clinical practice likely relate to patient and provider heterogeneity and the lack of published evidence. The benefit of TXA and/or prophylactic platelet transfusions would be best evaluated by a randomized controlled trial.

1. Introduction

Thrombocytopenia (platelets < 100 $\times 10^9$/L) is common and affects 40–65% of patients with myelodysplastic syndrome (MDS) [1]. The incidence and outcomes of patients with severe thrombocytopenia (platelets < 20 $\times 10^9$/L) is less well reported, but affects approximately 17% of patients [1], and is associated with increased bleeding [2] and higher risk Revised International Prognostic Scoring System (IPSS-R) scores [3]. Bleeding is an attributable cause of death in 13–24% of patients of patients with MDS [1,4].

Prophylactic (transfusions to asymptomatic patients for platelet counts below a set threshold) and therapeutic platelet (PLT) transfusions (for patients with bleeding) are commonly administered to prevent and treat bleeding in patients with MDS and severe thrombocytopenia [5]. However, they are associated with risks including bacterial contamination, allergic reactions, febrile non-hemolytic reactions, HLA alloimmunization, and refractoriness, in addition to costs and significant time commitment from patients [5,6].

At Sunnybrook Health Sciences Centre (Toronto, Canada), the administration of prophylactic and/or therapeutic PLT transfusions is at the discretion of the treating physician. Since 2006, we have generally adopted a therapeutic PLT transfusion practice (i.e. transfusion only for clinically significant bleeding) in severely thrombocytopenic MDS patients. Prophylactic PLT transfusions are generally instituted only after

* Corresponding author at: Odette Cancer Centre, Sunnybrook Health Sciences Center, 2075 Bayview Avenue, Toronto, Ontario, M4N 3M5, Canada.
E-mail address: rena.buckstein@sunnybrook.ca (R. Buckstein).

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a patient has experienced one or more clinically significant bleeding episodes. In lieu of prophylactic PLT transfusions, we commonly administer the antifibrinolytic tranexamic acid (TXA, 1–1.5 grams orally twice to three times per day) prophylactically to decrease minor mucosal bleeding and mitigate the use of platelet transfusions for non-severe bleeds. This is based on clinical experience, as there are no guidelines, definitive clinical trials, or established standards in this area [7].

There are few studies that assess the risk of bleeding related to persistent severe thrombocytopenia during the course of disease exclusively in a population of outpatients with MDS, and there are no studies reporting on the use of tranexamic acid as prophylaxis. Using the records of MDS patients at our centre, we conducted a retrospective review to evaluate the platelet transfusion practices, proportion of patients treated with tranexamic acid (TXA), and bleeding outcomes in patients with MDS and persistent severe thrombocytopenia.

2. Methods

Patients enrolled in the prospective national MDS registry (MDS-CAN) [4] and treated at Sunnybrook Health Sciences Centre in Toronto, Canada were included in the analysis. This registry collects patient and disease related characteristics, treatment responses and patient outcomes including bleeding and infections every 6 months. Eligibility included a diagnosis of MDS, MDS/myeloproliferative neoplasm (MPN), chronic myelomonocytic leukemia (CMML) and low blast (20–30%) acute myeloid leukemia (AML) (formerly known as RAEB-T) with persistent severe thrombocytopenia (PST) that was defined as a platelet count $< 20 \times 10^9$/L for at least 50% of laboratory measures for a minimum of an 8-week period. The area under the curve for plotted lab values for the entire PST observation period was used to determine whether 50% of days had PLTs $< 20 \times 10^9$/L for each patient. In addition to the prospectively collected data, we reviewed patients' electronic health records retrospectively for more granular data on bleeding events and dates of PST. The study was approved by the Sunnybrook institutional research ethics board.

Data collected included age, sex, date of diagnosis, date of death, WHO subtype and revised international prognostic score (IPSS-R) at time of onset of severe thrombocytopenia, chemotherapy and/or lenalidomide use within 4 weeks of or during the period of severe thrombocytopenia, start and end dates of TXA use, start and end dates of PST, platelet counts, red blood cell transfusion use, platelet transfusion frequency and quantity, and number and severity of bleeding events. Given the short half-life of transfused platelets, platelet transfusions were considered prophylactic (PROPH) if they occurred at a recurring interval of ≤ 2 weeks, and were considered therapeutic (THERA) otherwise. Bleeding events were rated using the World Health Organization bleeding scale [8], and recorded a maximum of once per clinic visit or inpatient hospital admission with the highest bleeding grade reported in the clinic note or discharge summary. Clinically significant bleeding events (CSBE) were considered to be WHO grade 2 or higher bleeding events [9].

Patients were split into four groups based on the maximal strategy used for prevention of bleeding, if the treatment was started at any time during their period of PST: Group 1 included patients who were treated with TXA alone; Group 2 included patients treated with TXA and PROPH; Group 3 included patients treated with PROPH alone; Group 4 included patients who received no prophylactic treatment for PST. Therapeutic platelet transfusions for bleeding episodes were documented when used for patients in Groups 1 or 4.

2.1. Statistics

Descriptive analyses on characteristics of demographics, thrombocytopenia and treatments were summarized in the whole cohort and by group, using frequencies and percentages for categorical variables, and median and interquartile ranges for continuous variables. To compare patient and clinical characteristics, Chi-square or Fisher Exact test was applied for categorical variables, and analysis of variance (ANOVA) was applied for continuous data, as appropriate. Bleeding outcomes were described by WHO grades 1–4 in the whole cohort and by group, and Chi-square or Fisher Exact test was also used for comparisons among 4 groups. Overall survival (OS) was defined as time from the start date of PST to death from any cause. Kaplan-Meier method was used to estimate the probability of OS with 95% confidence intervals (CI), and actuarial median OS years were calculated for each of the 4 groups. Log-rank test was used to compare OS curves among the 4 groups. Statistical significance was chosen as p-value < 0.05. All analyses were conducted by using SPSS version 24, or R package (version 3.5.0).

3. Results

3.1. Demographic data

Out of 581 total patients in the registry at data extraction, 200 patients had a PLT count $< 20 \times 10^9$/L at any time. 99 (50%) of these 200 patients met the criteria for PST and were included in the analysis. Demographic data are presented in Table 1. There were no significant differences in characteristics between the groups with the exception of increased rates of RBC transfusion dependence in groups 1 and 2 compared with groups 3 and 4. Twenty-nine (29%) of 99 PST patients had no platelet transfusion prescribed during the median follow-up period of 27 weeks.

3.2. Treatments used for thrombocytopenia

Each patient's individual course during the period of their PST is shown in Fig. 1. Demarcations in colour indicate change in thrombocytopenia management, and 'X's indicate Grade 3 or 4 bleeding events. For patients who received TXA prophylaxis, TXA began after a median of 6 (IQR 0–13) or 4 weeks (IQR 0–13) after onset of PST for Groups 1 (TXA) and 2 (TXA + PROPH) respectively. For patients receiving PROPH, prophylactic PLTs were initiated within 8 weeks (IQR 2–15) (Group 2, TXA + PROPH) or 2 weeks (IQR 0.6–8) (Group 3, PROPH) from the onset of PST.

32% of patients (n = 9) in Group 1 (TXA), and 23% (n = 3) in Group 4 (NO TX) required therapeutic platelet transfusions during their severe thrombocytopenic period, while the remaining 71% (n = 29) did not require any platelet transfusions during this time. Patients in groups 1 and 4 who were transfused with platelets received them less frequently (every 2.8 and 4 weeks respectively) compared with patients in groups 2 and 3 (every 0.7 and 0.9 weeks respectively), p = 0.004. Similarly, the number of platelet transfusion events per 4-week period (see Table 2) was significantly reduced in groups 1 and 4 compared with groups 2 and 3.

3.3. Bleeding outcomes

In patients who had a bleeding event of any grade (83%), there was a median of 6 weeks (IQR 0–12) from the onset of their PST to their first bleeding event. See Table 3 for bleeding outcomes by grade.

Of the 12 patients who experienced grade 3 or 4 bleeding, 75% (6/8 patients) of patients on PROPH (Groups 2 and 3) had platelet refractoriness, while 0 (0/4) patients on TXA alone (Group 1) had platelet refractoriness. 75% (9/12 patients) of these patients were on chemotherapy during or within 4 weeks prior to their PST.

3.4. Overall survival

Actuarial median overall survival of the cohort was 0.9 years (95% CI 0.7–1.2) (Fig. 2). Survival differed by group (Group 1: 1.2 years (95% CI 0.7–2.4), Group 2: 0.7 years (95% CI 0.5–1.2), Group 3: 0.6

Table 1
Patient Characteristics.

	All (n = 99)	Group 1 TXA only (n = 28)	Group 2 TXA + PROPH (n = 39)	Group 3 PROPH only (n = 19)	Group 4 No tx (n = 13)	p-value
Age at diagnosis of MDS (years)	72 (65-77)	71 (67-75)	72 (65-77)	74 (64-77)	72 (63-77)	0.97
Age at death (years)	75 (70-80)	76 (71-79)	74 (71-80)	76 (69-81)	75 (74-79)	0.98
Sex (F, %)	38% (38)	32% (9)	39% (15)	37% (7)	54% (7)	0.26
Follow-up duration (years)	0.8 (0.5-1.9)	1.2 (0.7-2.3)	0.6 (0.5-1.3)	0.6 (0.3-1.3)	2.1 (0.9-3.2)	–
Actuarial survival (years) (95% CI reported)	0.9 (0.7-1.2)	1.2 (0.7-2.4)	0.7 (0.5-1.2)	0.6 (0.3-1.3)	2.5 (0.9-7.4)	**0.04**
IPSS-R* Score						0.13
Very low	4% (3)	5% (1)	0	0	20% (2)	
Low	10% (7)	10% (2)	8% (2)	20% (3)	0	
Intermediate	26% (19)	43% (9)	23% (6)	7% (1)	30% (3)	
High	31% (22)	29% (6)	27% (7)	40% (6)	30% (3)	
Very High	29% (21)	14% (3)	42% (11)	33% (5)	20% (2)	
WHO Subtype						0.16
SLD	4% (4)	11% (3)	0	0	8% (1)	
MLD	29% (26)	14% (4)	35% (6)	25% (6)	42% (5)	
RS-MLD	2% (2)	0	3% (1)	6% (1)	0	
5delq	3% (3)	0	3% (1)	0	17% (2)	
EB-1 or 2	32% (29)	39% (11)	30% (10)	35% (6)	17% (2)	
MPN	1% (1)	4% (1)	0	0	0	
CMML-1 or 2	7% (6)	11% (3)	3% (1)	0	17% (2)	
Unclassificable	7% (6)	11% (3)	6% (2)	6% (1)	0	
Secondary-AML or tAML	14% (13)	11% (3)	21% (7)	18% (3)	0	
Primary physician						0.15
1	66% (65)	50% (14)	51% (20)	16% (3)	8% (1)	
2	39% (39)	21% (6)	26% (10)	68% (13)	77% (10)	
All others (3-9)	22% (22)	29% (8)	23% (9)	16% (3)	16% (2)	
RBC dependent	42% (42)	54% (15)	51% (20)	21% (4)	23% (3)	**0.01**
Chemotherapy use during preceding 4 weeks or during						0.18
Any chemotherapy	60% (59)	57% (16)	69% (27)	53% (10)	46% (6)	
Lenalidomide use	11% (11)	14% (4)	8% (3)	5% (1)	23% (3)	
Characteristics of thrombocytopenia						
Years from diagnosis to onset of durable severe thrombocytopenia	0.9 (0.2-2.2)	1.2 (0.3-2.6)	0.5 (0.1-1.6)	1.2 (0.4-2.1)	1.0 (0.2-2.6)	0.8
Duration of thrombocytopenia (weeks)	27 (16-49)	36 (19-71)	24 (18-46)	23 (11-33)	16 (13-47)	0.2
Median platelet count	12 (9-16)	13 (9-17)	10 (8-15)	13 (11-17)	13 (11-16)	0.3
Percent of measured lab tests with PLT $< 10 \times 10^9$/L	39% (17%-63%)	36% (7%-67%)	50% (25-67%)	36% (27-50%)	23% (14-50%)	0.2

Median (IQR) is reported unless otherwise indicated.
*IPSS-R; Revised International Prognostic Scoring System.
SLD: Single lineage dysplasia; MLD: Multilineage dysplaia; RS-MLS: Ringed-sideroblasts with multilineage dysplasia; EB: Excess blasts; MPN: Myeloproliferative neoplasm; CMML: chronic myelomonocytic leukemia; tAML: Therapy-related acute myelogenous leukemia.

years (95% CI 0.3–1.3), Group 4: 2.5 years (95% CI 0.7–7.4)), with patients who had received no prophylactic treatments for their thrombocytopenia (Group 4) living longest (p = 0.04).

During the entire period of follow up, the cause of death was hemorrhage in 9% of patients (n = 9), compared to 7% of patients in the entire MDS registry (20 out of 272 deaths, out of 581 total patients in the registry). Four of these deaths occurred during the period of PST including one patient in Group 1 (intracranial bleed, PLT count 5×10^9/L on date of death), two patients in Group 2 (gastrointestinal and genitourinary bleeding, PLT counts 19×10^9/L and 2×10^9/L respectively on date of death, both were platelet refractory), and one patient in Group 3 (gastrointestinal bleeding, PLT count 9×10^9/L on date of death, patient was platelet refractory). Two deaths occurred shortly after the period of PST for two patients in Group 1 (one death occurred 23 days after a Grade 4 intracranial bleeding event, PLT count at time of death 10×10^9/L; the other death occurred 22 days after the end of PST, type of bleed unknown, last known PLT count 4×10^9/L prior to death). Three deaths attributed to haemorrhage occurred well outside the period of PST (one had no details on type nor a recent platelet count, and two deaths were related to intracranial haemorrhage with PLT counts of 17×10^9/L and 79×10^9/L). The latter patient with a PLT count of 79×10^9/L presented with cerebral venous sinus thrombosis and cerebral infarction, with hemorrhagic conversion after starting intravenous heparin.

4. Discussion

This retrospective cohort study from a single tertiary-care institution demonstrated heterogeneous practice in the management of PST with 58% of patients eventually receiving prophylactic platelet transfusions, 12% receiving only therapeutic PLT transfusions, 19% receiving only TXA, and 10% requiring no treatment for their thrombocytopenia. While there are clearly some uncaptured patient characteristics or events to explain these differences other than physician preference, it is important to note that the rates of major bleeding were low in this cohort with only 6% of patients with PST experiencing a Grade 4 bleed despite a median PLT count of 12×10^9/L. A disheartening message is the significantly short survival associated with PST (median 0.9 years) validating the prognostic importance of severe thrombocytopenia in the IPSS-R and other prognostic models.

No paper has previously reported on the rates of bleeding during the period of PST in patients with MDS, though one can extrapolate from the control arms of recent randomized trials of eltrombopag or romiplostim in patients with low-risk MDS and severe thrombocytopenia [9,10]. Notably these patients had higher platelet counts (baseline PLT count in both studies 18×10^9/L) compared to 12×10^9/L in our cohort, and all had low risk MDS. In the trial by Oliva and colleagues, 42% of patients in the control arm had at least one CSBE, and there were a total of 57 CSBEs in 13 patients over the 24-week follow-up period [9]. In the trial by Giagounidis and colleagues, there were 161 CSBE over the 26-week follow-up period of 83 patients in the control arm [10].

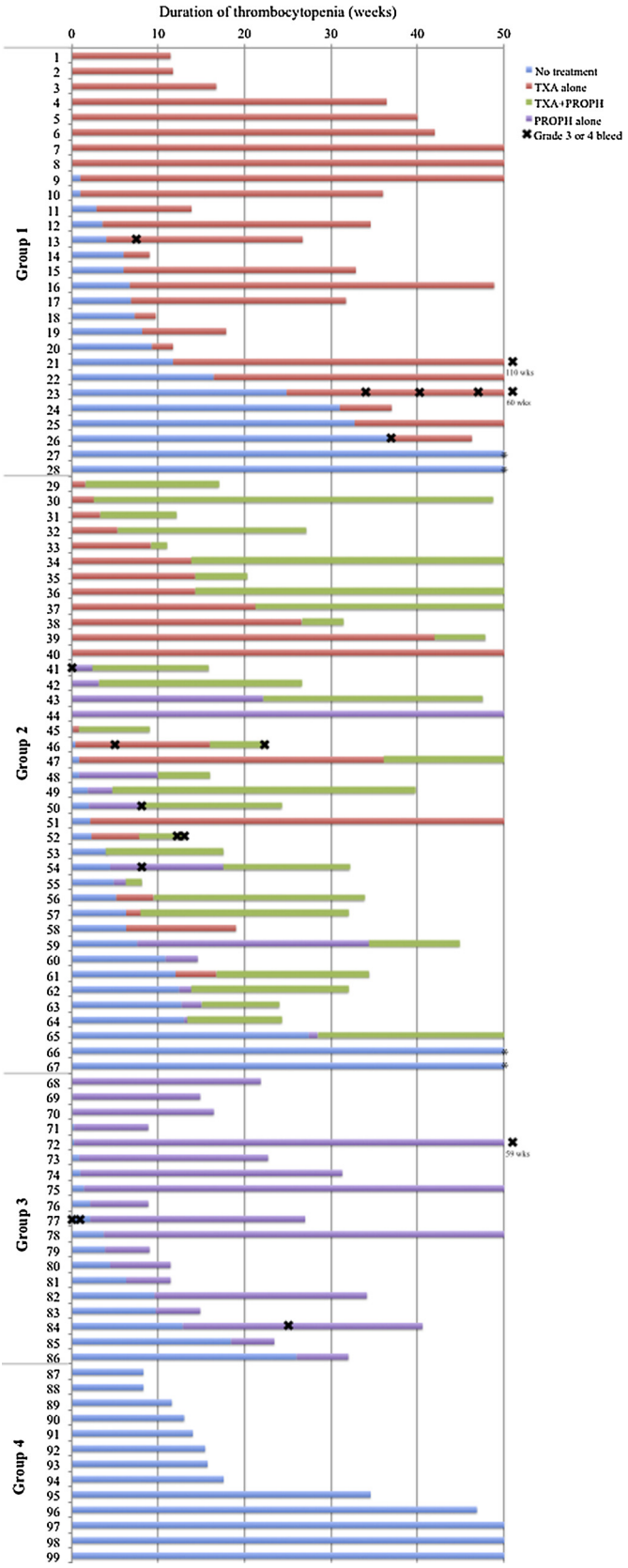

Fig. 1. illustrates the course of each patient's prophylactic treatment to prevent bleeding during PST. The graph axis extends to 50 weeks, which is the third quartile of duration of PST (IQR 75). Any Grade 3 or 4 bleeds that occurred outside this period are denoted at the edge of the graph with the time of event occurrence after onset of PST. The patient's maximal prophylactic treatment category resulted in their group assignment (indicated on the y-axis), and the colour corresponding to that treatment may be cut off by the graph axis.
*Note that these patients began treatment with TXA, PROPH, or TXA + PROPH after at least 50 weeks of no treatment, which is why no treatment course appears on the graph. Patient 27 had 73 weeks of no treatment followed by 18 weeks of TXA; patient 28 had 188 weeks of no treatment followed by 345 weeks of TXA; patient 66 had 57 weeks of no treatment, then 26 weeks TXA alone, then 2 weeks TXA + PROPH; patient 67 had 157 weeks of no treatment, then < 1 week PROPH alone, then 119 weeks PROPH + TXA

These rates are similar to our findings, where 44% of patients had at least one CSBE, and there were 79 CSBEs occurring in 44 patients over the median 27-week period of PST.

Despite major bleeding occurring at low rates of 6% during the period of PST, the consequence of major bleeding is not negligible as 4% of patients died as a result of hemorrhage that occurred during their PST, and a further 2% died as a result of hemorrhage occurring shortly after their period of PST. This is similar to the previous randomized trials which showed that 0–4% of patients in the placebo arm died as a result of hemorrhage during the period of study follow up [9,10], and similarly our own MDS registry in which 7% of all patients with a known cause of death died from hemorrhage. Three of four deaths during the PST occurred in patients already transitioned to receiving prophylactic platelets (Fig. 1), and all three of these patients were noted as refractory to platelets, likely on the basis of alloimmunization from chronic platelet transfusions. We also found that 3% of patients died with hemorrhage occurring well outside the period of PST. Interestingly, most patients who died of hemorrhage had a PLT count $< 10 \times 10^9$/L at the time of death; however it is important to note that three out of nine had a platelet count well over 10×10^9/L at the time of death, which suggests significant bleeds can still occur above target platelet counts. This is not unexpected, as there are many other factors that increase bleeding risk in MDS including platelet dysfunction, treatments, infection risk, or anemia [2,11,12].

In patients on chemotherapy for hematologic malignancy, including those with acute myeloid leukemia, it is clear that prophylactic platelet transfusions have a role in reducing the rates of Grade 2–4 bleeding compared to no prophylaxis (CSBE in 50% in no prophylaxis group vs. 43% with prophylaxis), although the rates of grade 3–4 bleeding within this high risk patient population were low (1–2% vs. < 1%) [13]. Contrastingly, in patients with hematologic malignancy after autologous stem cell transplantation, a therapeutic platelet transfusion strategy is safe [14] and is endorsed in a guideline by the American Society for Clinical Oncology [15]. For MDS, the standard of care for outpatients with MDS and PST has not been established, and there are no evidence-based data guiding management. This leads to variations in care, which were observed even within this single-centre study. From the present study, it is clear that some patients may have no significant (or any) bleeding while using TXA, or even no treatment.

For example, 66% (27 of 41 patients) of severely thrombocytopenic patients on TXA or no therapy required no therapeutic platelet transfusions and had no Grade 3 or 4 bleeding events despite having a median PLT count of 16×10^9/L, and PLT $< 10 \times 10^9$/L 23% of the time. Furthermore, 46% (19 of 41 patients) of these patients experienced no Grade 2 bleeding. This suggests that some patients can be safely managed without prophylactic platelet transfusions. Further studies are warranted to determine clinical or laboratory parameters predictive of bleeding.

This study also makes it clear that prophylactic platelet transfusions are not without risk, as six of eight patients who had major bleeding while receiving prophylactic platelet transfusions were refractory to transfusions, and three of them died of hemorrhage. The minimal costs and risks of TXA compared to the financial burden, risks, and resource utilization of platelet transfusions must not be overlooked. Utilizing

Table 2
Characteristics of treatments.

	All (n = 99)	Group 1 TXA only (n = 28)	Group 2 TXA + PROPH (n = 39)	Group 3 PROPH only (n = 19)	Group 4 No tx (n = 13)	p-value
Time from thrombocytopenia to first bleeding event (weeks)	6 (0-12)	10 (4-21)	5 (0-10)	3 (0.1-9)	5 (0-16)	**0.046**
Time from thrombocytopenia to use of TXA (weeks)		6 (0-13)	4 (0-13)	–	–	0.5
Time from thrombocytopenia to use of PROPH (weeks)		–	8 (2-15)	2 (0.6-8)	–	0.2
Platelet transfusion use						
Percent needing platelet transfusions						
Prophylactic	59% (58)	0	100% (39)	100% (19)	0	**0.011**
Therapeutic	12% (12)	32% (9)	0	0	23% (3)	
Median duration between platelet transfusions (weeks)	0.86 (0.5-1.1)	2.8 (2.5-6.8)	0.7 (0.5-1.0)	0.9 (0.5-1.0)	4.0 (2.2-5.7)	**0.004**
Number of platelet transfusions events per 4-week period	1.18 (0-2.8)	0 (0-0.1)	2.2 (1.4-3.0)	3.1 (2.2-5.2)	0 (0-0.3)	< **0.0001**

Median (IQR) is reported unless otherwise indicated.

alternative and safe therapy to platelet transfusions, if one can be demonstrated in a prospective trial, would have significant economic benefits and may improve quality of life by minimizing visits to hospital for transfusion.

This study has several limitations. Although the prospective MDS registry was used for most of the data collection, some data were obtained retrospectively, which may be subject to bias and incomplete information. Although our registry has a low loss to follow-up of 3.7%, 11% of patients included in this analysis had an unknown cause of death (compared to 17.3% unknown cause of death in the entire registry). This may result in an underestimate of the rate of deaths from hemorrhage. Our classification of prophylactic versus therapeutic platelet transfusion using a cut-point of frequency ≤ 2 weeks was arbitrarily chosen for categorization, although it has biologic plausibility. Although the groups were similar in most of their baseline characteristics, there were likely unmeasured confounders causing heterogeneity between groups. For example, one could postulate that more phenotypically severe cases, as reflected by higher rates of RBC transfusion dependence were treated with prophylactic platelet transfusions, and that phenotypically less severe patients received no treatment. However, as this was a descriptive study, no conclusions were made regarding a causative association between the treatments used and the outcomes observed. Our small sample size limits statistical power and generalizability of the findings.

In conclusion, patients with MDS and persistent severe thrombocytopenia at a tertiary care centre had low rates of major bleeding (6%) but poor overall survival (0.9 years). A number of patients who did experience severe bleeding had platelet refractoriness attributable to prophylactic platelet transfusion use at the time of their hemorrhage.

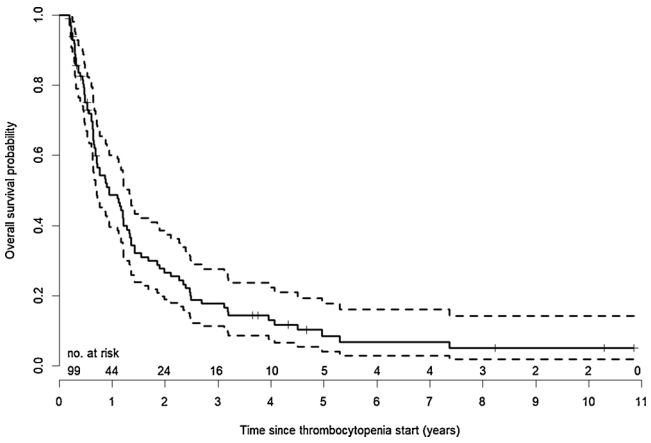

Fig. 2. Overall Survival of Cohort with 95% CI.

Patients were heterogeneous in their treatments and bleeding events, suggesting that patient factors and physician preferences may account for these differences. Furthermore, there were disparate practices amongst treating physicians even in this single-centre trial, likely related to the lack of published evidence in treating patients with MDS and thrombocytopenia.

As there appears to be clinical equipoise in the methods for prevention of bleeding in patients with MDS and persistent severe thrombocytopenia, the benefit of TXA and/or prophylactic platelet transfusions would be best evaluated by a randomized controlled trial. The low rates of severe bleeding in this retrospective analysis suggest

Table 3
Bleeding Outcomes.

	All	Group 1	Group 2	Group 3	Group 4	p-value
Number of patients with any bleeding event	82% (81)	86% (24)	74% (29)	89% (17)	85% (11)	**0.006**
Number of bleeding events per 8-week period						
Any	0.48 (0.13-0.96)	0.46 (0.14-0.73)	0.89 (0.35-1.29)	0.26 (0-0.70)	0.17 (0-0.46)	**0.002**
Grade 1	0.25 (0-0.66)	0.18 (0-0.47)	0.50 (0.09-0.87)	0 (0-0.38)	0.10 (0-0.46)	0.08
Grade 2	0 (0-0.24)	0 (0-0.17)	0.21 (0-0.5)	0 (0-0)	0 (0-0)	**0.03**
Grade 3	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.6
Grade 4	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0 (0-0)	0.6
Percentage of patients experiencing bleeding event						
Grade 1	67% (147 events in 67 pts)	71% 46 events in 20 pts	79% 75 events in 31 pts	47% 12 events in 9 pts	54% 14 events in 7 pts	0.07
Grade 2	41% (62 events in 41 pts)	43% 17 events in 12 pts	59% 39 events in 23 pts	21% 4 events in 4 pts	15% 2 events in 2 pts	**0.02**
Grade 3	8% (12 events in 8 pts)	7% 4 events in 2 pts	10% 5 events in 4 pts	11% 3 events in 2 pts	0	0.6
Grade 4	6% (6 events in 6 pts)	11% 3 events in 3 pts	5% 2 events in 2 pts	5% 1 event in 1 pt	0	0.07

Median (IQR) is reported unless otherwise indicated.

that conduct of such a prospective trial would not place undue risk on enrolled patients.

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