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Research paper

Indications and use of, and incidence of major bleeding with, antithrombotic agents in myelodysplastic syndrome

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ABSTRACT

Myelodysplastic syndrome (MDS) and antithrombotic medication both increase the risk of bleeding. We set out to analyze the prevalence of use, indications and bleeding risk of antithrombotic therapy in patients with MDS in a retrospective, single-center study including all patients with MDS with > 20×10^9/L platelets. 193 patients (59% male, median age 75 years) were included; 122 did not receive antithrombotic treatment, 51 received antiplatelet agents and 20 received anticoagulants. The cumulative incidence of major bleeding was higher in both the antiplatelet group (11.8% at 4 years, 95% confidence interval [95%CI]: 4.7–22.3%) and the anticoagulation group (21.2% at 4 years, 95%CI 6–42.5%) than in the control group (2.8% at 4 years 95%CI: 0.7–7.3%). The prevalence of use of antithrombotic medication in this cohort of patients with MDS was high and bleeding risk was increased in these patients.

1. Introduction

Myelodysplastic syndromes (MDS) are a heterogeneous group of clonal disorders of the myeloid stem cell. They are generally a disease of the elderly and they are clinically characterized by cytopenias, including thrombocytopenia [1]. A large retrospective study of patients with MDS found bleeding to be the cause of death of around 10% of patients with MDS and to increase notably when platelet count was lower than 20×10^9/L [2].

Antithrombotic drugs, including antiplatelet agents and anticoagulants, are widely prescribed for a variety of indications, particularly of a cardiovascular nature. The prevalence of disorders for which antithrombotic drugs are recommended increases with age [3–5]. Based on this, one could imagine that the use of antithrombotic drugs is common in patients with MDS but this has not been well examined. Therefore, we set out to assess the prevalence of use of antithrombotic drugs in patients with MDS, the indications for which they were prescribed and the incidence of major bleeding in these patients.

2. Material and methods

This is a retrospective study assessing the indications, the actual use and the side effects of antithrombotic agents in adult patients with MDS or MDS/Myeloproliferative neoplasms (MPN) diagnosed and/or treated in a single institution between 2008 and 2017. All consecutive patients were considered for inclusion but were finally excluded if their platelet count at diagnosis was < 20×10^9/L or if they were receiving antiplatelet agents due to thrombocytosis (which occurred in a few cases of MDS/MPN). A medical chart review of all MDS patients was carried out and relevant demographic and clinical data were extracted, with particular emphasis on the use of antithrombotic agents and bleeding events.

The cohort was divided according to the use of antiplatelet agents, anticoagulant agents or no antithrombotic treatment (control group) at the time of the diagnosis of MDS. Patients treated with dual antiplatelet therapy (n = 4, all temporarily) were included in the antiplatelet group and one patient receiving both anticoagulant and antiplatelet therapy was included in the anticoagulant group.

The main endpoint was the incidence of major bleeding as defined

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by the International Society for Thrombosis and Haemostasis (ISTH) with a slight modification. The ISTH defines major bleeding as a fatal bleed, one occurring in a critical organ, causing a fall in hemoglobin of ≥20 g/L or requiring transfusion of ≥2 units of red cells [6]. We did not include this latter criterion (requirement of ≥2 units of red cells), as we deemed patients with MDS to be more likely to receive red cell transfusion given their frequent baseline anemia. A drop in hemoglobin ≥20 g/L was still considered a major bleeding. We also excluded bleeding events clearly related to an invasive procedure as bleeding risk would then depend strongly on such procedures rather than on the antithrombotic effect of the studied drugs.

Frequencies and percentages are given for categorical variables and median and interquartile range for quantitative variables. The groups were compared by means of the Chi-squared and the Kruskal–Wallis test, as appropriate.

The cumulative incidence of major bleeding was analyzed by means of a competing risk model (Gray's test [7,8]), considering major bleeding as the main event and a combined endpoint of transformation into acute leukemia, platelet count $< 20 \times 10^9$/L, start of intensive chemotherapy/stem cell transplantation, change of antithrombotic agent (start of a new drug, discontinuation of the group-defining one or change from anticoagulant to antiplatelet or vice versa) or death without major bleeding as the competing risk. This combined endpoint was chosen as we considered that patients who fulfilled any of the endpoints in the competing risk would generally be unlikely to start standard antithrombotic medication even if indicated. Importantly, follow-up also stopped after the first bleeding event given that multiple bleedings in a patient with a predisposing condition could lead to a falsely increased incidence of bleeding. Median follow-up was determined by the reverse Kaplan-Meier method. R software and the EZ-R package, version 1.37 [9] were used for all analyses.

3. Results

3.1. Patients

There were 193 patients; 122 (64%) in the control group, 51 (26%) in the antiplatelet group and 20 (10%) in the anticoagulation group. Table 1 shows their baseline characteristics. Briefly, most patients were male (113/193, 59%) with a median age of 75 (interquartile range 66–81) and the platelet count at diagnosis was $> 100 \times 10^9$/L in 134/191 (70%). Ischemic heart disease (IHD) and atrial fibrillation (AF) were the main indications for antiplatelet therapy (24/51, 47%) and for anticoagulation (18/20, 90%), respectively.

3.2. Bleeding episodes

With a median follow-up of 4.88 years (95%CI 2.24–6.10), there were 14 episodes of major bleeding among the 193 patients.

In the control group there were 4 episodes of major bleeding; 2 gastrointestinal hemorrhages, one intracranial bleeding and one hematoma in the upper leg. Two of them occurred with normal platelet counts and the other two with 37 and 61×10^9/L, respectively. One of them (intracranial bleeding) led to the death of the patient.

There were 7 episodes of major bleeding in the antiplatelet group; 2 intracerebral hemorrhages (platelet count 91 and 37×10^9/L, both leading to the death of the patient), 2 episodes of epistaxis (one with 68×10^9/L and one with normal platelet count) and 3 gastrointestinal bleeding episodes, all with normal platelet counts.

Finally, there were 3 episodes of major bleeding in the anticoagulation group; one abdominal bleeding in the setting of severe sepsis (with INR > 10 and normal platelet count) leading to the death of the patient, one intracranial hemorrhage (platelet count: 45×10^9/L) and one gastrointestinal bleeding in a patient receiving both low molecular weight heparin and aspirin due to a pulmonary embolism and a coronary stent (platelet count 37×10^9/L).

Overall, 4 of the 14 (29%) major bleeding episodes led to death.

Table 1
Characteristics of the patients included in this study assessing bleeding in myelodysplastic syndrome (MDS) based on antithrombotic therapy.

		No antithrombotic (n = 122)	Antiplatelet (n = 51)	Anticoagulant (n = 20)	p value
Male, n (%)		63 (52)	36 (71)	14 (70)	0.038
Age (years), median, (IQR)		73.3 (63.9–79.7)	75 (68.1–82)	81.8 (77–84)	< 0.001
Charlson comorbidity index, median (IQR)		0 (0–1)	1 (1–2)	1 (1–2)	< 0.001
Diagnosis	MDS with < 5% blasts	66 (54)	29 (56)	12 (60)	0.912
	MDS with ≥5% blasts	26 (21)	9 (18)	3 (15)	
	CMML	21 (17)	11 (22)	3 (15)	
	non-CMML MDS/MPN	8 (7)	2 (4)	2 (10)	
Platelet count at diagnosis (x10^9/L)[a]	20–50	13 (11)	2 (4)	1 (5)	0.400
	51–100	29 (24)	9 (18)	3 (15)	
	> 100	80 (66)	38 (75)	16 (80)	
Indication for antithrombotic treatment	Atrial fibrillation	–	6 (12)	18[b] (90)	–
	Ischemic heart disease	–	24 (47)	–	–
	Cerebrovascular disease	–	7 (14)	1 (5)	–
	Primary prevention	–	4 (8)	–	–
	PAD	–	4 (8)	–	–
	VTE	–	1 (2)	2[b] (10)	–
	Other	–	5[c] (10)	–	–
Agent	ASA	–	39 (76)	1[d] (5)	–
	clopidogrel	–	8 (16)	–	–
	DAPT	–	4 (8)	–	–
	VKA	–	–	19 (95)	–
	LMWH		–	1[d] (5)	–

IQR: Interquartile range, CMML: chronic myelomonocytic leukemia; MPN: Myeloproliferative neoplasm, PAD: peripheral artery disease; VTE: Venous thromboembolic disease; ASA: Acetylsalicylic acid; DAPT: Dual antiplatelet therapy; VKA: vitamin K antagonists.LMWH: Low molecular-weight heparin.

[a] Data was unavailable for 2 patients in the antiplatelet group.

[b] One patient received anticoagulation for both atrial fibrillation and VTE.

[c] Aortic valve replacement (n = 2), lenalidomide treatment (n = 2), unknown (n = 1).

[d] One patient received both antiplatelet and anticoagulant therapy (LMWH due to thrombocytopenia) due to recent VTE and coronary stent.