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ORIGINAL ARTICLE

Frequency of venous thrombotic events in patients with myelodysplastic syndrome and 5q deletion syndrome during lenalidomide therapy

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Abstract

Lenalidomide is known to increase the risk of venous thromboembolism in patients with hematologic malignancies. The role of antithrombotic prophylaxis in patients receiving lenalidomide is well established in multiple myeloma. However, when used in patients with a myelodysplastic syndrome (MDS)—in particular, del(5q) patients—the risk of venous thromboembolism and the need for anticoagulation are unknown. We performed a retrospective for MDS patients with 5q deletion. The total number of patients was 64, and 24 (38%) were treated with lenalidomide. Of those who received lenalidomide, venous thrombotic events (VTE) occurred in 4 (17%). All events occurred after 1 year of lenalidomide therapy. Although limited by the cohort size, concurrent erythropoietin-stimulating agents (ESAs) were not associated with increased thrombotic events, and the diagnosis of VTE did not affect survival. Our data suggest an increased incidence of VTE with prolonged lenalidomide treatment, mainly if MDS responds to this therapy.

Keywords MDS · VTE · Lenalidomide

Introduction

5q deletion syndrome has been recognized as a specific entity in myelodysplastic syndromes (MDS) since 2001, with the World Health Organization (WHO) revision of myeloid neoplasm classification. It was described as having isolated 5q deletion, anemia, normal or increased platelets, bone marrow blast less than 5%, no Auer rods, and normal to increased megakaryocytes with hypolobated nuclei [1]. Lenalidomide has been approved by the US Food and Drug Administration (FDA) for MDS transfusion-dependent anemia with del(5q) abnormality, although most of the responses were seen in the low- and intermediate-1 International Prognosis Scoring System (IPSS) categories [2]. The main clinical trial that led to FDA approval showed an erythroid response rate of up to 76% [3, 4]. Additionally, it has been demonstrated that lenalidomide has activity in non-5q deletion MDS patients with the same IPSS category [5, 6]. In 2016, MDS with del(5q) criteria was revised again by the WHO to allow one cytogenetic abnormality unrelated to chromosome 7 [7], while keeping the bone marrow blast count less than 5%. This revision allows patients with refractory anemia with ring sideroblasts, refractory anemia with unilineage, or multilineage dysplasia to be included in the MDS del(5q) category if they fit these criteria.

The thrombotic adverse events of lenalidomide have been described in reports of multiple myeloma (MM), non-Hodgkin lymphoma, and MDS. The current recommendations are to pursue antithrombotic prophylaxis in the absence of contraindication [8]. A systematic review by Lian et al. [9] investigated the safety of lenalidomide for low- and intermediate-1–risk MDS with or without 5q deletion and reported deep vein thrombosis (DVT) as grade III–IV adverse events of 3% (95% CI, 2–5%). The increased risk of thrombosis is related not only to the drug effects of lenalidomide but also to host factors, including comorbidities associated with the age group of MDS patients, normal-to-elevated platelet counts in 5q deletion, or the presence of a contraindication to antithrombotic prophylaxis.

Another thrombotic risk factor, studied by Smith et al. [10], is the use of erythropoietin-stimulating agents (ESAs). In their case-crossover study, which used the US Surveillance, Epidemiology, and End Results (SEER) Medicare-linked

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database, no statistical association was shown between ESA and thrombosis (as already known, MDS del(5q) patients are likely to fall into the low- and intermediate-1 score category by IPSS, and those groups are considered candidates for hematopoietic growth factor as a frontline therapy). Although, that was not the case in MM during trials investigating lower dexamethasone dose and when combined with ESA [11]. Also, lenalidomide has been shown to restore erythropoietin responsiveness [12]. To obtain more validated results, Komrokji et al. [13] studied this combination prospectively in a phase I/II trial and reported no increase in the rate of DVT risk in the del(5q) group. Currently, this combination is being investigated by a phase III trial sponsored by the ECOG-ACRIN Cancer Research Group E2905. At the time of their abstract presentation at the annual American Society meeting in 2016, no difference in adverse events had been reported among the 248 patients enrolled in their study [14].

We hereby report a single-institution experience of venous thrombotic events (VTE) in patients with MDS using lenalidomide.

Materials and methods

This is a retrospective chart review study from a single-institution database. We performed data extraction from Mayo Clinic electronic health records from October 1993 through March 2016, with updated follow-up until August 2017. MDS diagnosis was confirmed by central hematopathologic review, and cytogenetic information was obtained. Data sets were extracted, along with bone marrow biopsy and aspirate reports, to verify the del(5q) with or without 1 additional abnormality (except for monosomy 7 or del [15]), and bone marrow blasts < 5%. Appropriate approval was obtained from the Mayo Clinic Institutional Review Board. Baseline characteristics including age, sex, bone marrow blast, and complete blood count at diagnosis were obtained, and the IPSS and revised-IPSS (R-IPSS) scores were calculated. Treatment outline focused on whether patients received lenalidomide or concurrent ESA, as well as treatment duration. The clinical outcomes of this cohort were assessed by overall survival (measured from time of diagnosis until last follow-up or death), progression to acute myeloid leukemia (AML)—time to AML (measured from time of diagnosis until AML diagnosis)—and hematological response–erythroid (HI-E) as defined by the International Working Group for MDS (IWG) in 2006 [16].

The diagnosis of venous thromboembolism during lenalidomide therapy, including pulmonary embolism (PE) and DVT, was confirmed by computed tomography (CT) or venous Doppler ultrasound, respectively. The VTE was captured as an event during lenalidomide. Univariate and multivariate analysis was used for prognostic factors; Fisher's exact test was used for categorical variables and the Wilcoxon rank sum

Table 1 Clinical, laboratory, and outcome features of the study cohort of all patients

Number of patients	64
Age, median (range), year	72.5 (38–87)
Sex, %	
Male	40
Female	60
CBC at diagnosis, median (range)	
Hemoglobin (g/dL)	9.5 (4.7–12.6)
WBC ($\times 10^9$/L)	4.5 (0.9–16)
ANC ($\times 10^9$/L)	2.1 (0.03–73.5)
Platelets ($\times 10^9$/L)	187 (12–838)
Bone marrow blast, median (range), %	2 (2–4)
R-IPSS cytogenetics, %	
Good	97
Intermediate	3
R-IPSS group, %	
Very low	26
Low	62
Intermediate	12
Lenalidomide treatment, %	38
Duration of lenalidomide treatment, median (range), months	10.5 (1–44)
Transformation to AML, %	10
Time to AML, median (range), months	41.5 (10–116)
CBC before starting lenalidomide, median (range)	
Hemoglobin (g/dL)	8.3 (4.7–11.4)
WBC ($\times 10^9$/L)	4 (1–9.5)
Platelets ($\times 10^9$/L)	190 (24–805)
CBC at response (HI-E), median (range)	
Hemoglobin (g/dL)	11.7 (8.9–14.3)
WBC ($\times 10^9$/L)	3 (1.58–6)
Platelets ($\times 10^9$/L)	127 (68–324)
Median OS, months (range)	52 (0.2–218)
Patients on antithrombotic prophylaxis, no. (%)	37 (58)
Antiplatelet	28 (76)
Anticoagulation	8 (22)
DOAC	1 (3)
Indications for long-term anticoagulation prior to VTE diagnosis, no. (%)	
Atrial fibrillation	6 (67)
History of VTE	2 (22)
Antiphospholipid syndrome	1 (11)
VTE, no. (%)	6 (10)
PE, no. (%)	2 (33)
DVT, no. (%)*	5 (83)

*One patient had PE and DVT

ANC, absolute neutrophilic count; *R-IPSS*, Revised International Prognostic Scoring System; *HI-E*, hematological improvement–erythroid; *DOAC*, direct oral anticoagulant; *VTE*, venous thromboembolism; *PE*, pulmonary embolism; *DVT*, deep vein thrombosis

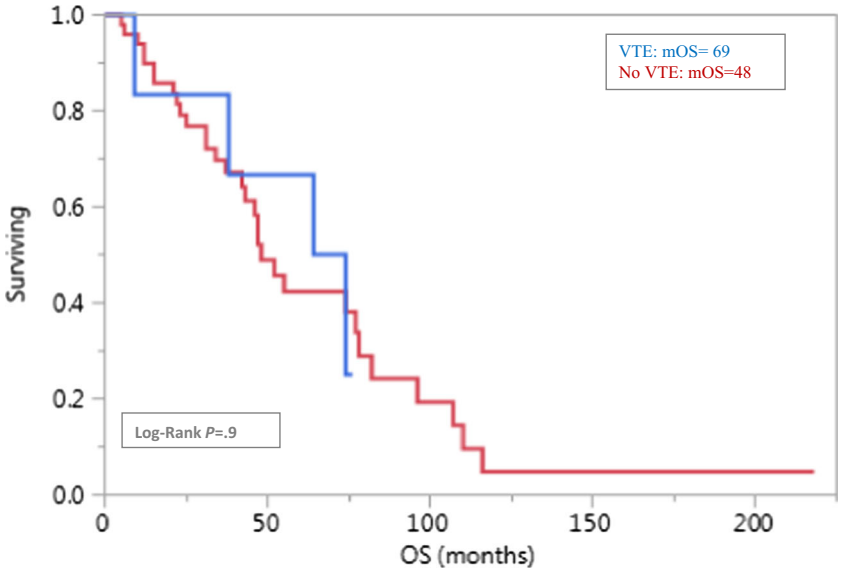

Fig. 1 Overall survival for all MDS patients ($N = 64$) with 5q deletion syndrome. mOS indicates median overall survival; OS, overall survival; VTE, venous thromboembolism

test for continuous variables. Overall survival was estimated by using the Kaplan-Meier methods and curves were compared using the log-rank test. Data analysis was done using JMP software version 13, SAS Institute Inc., Cary, NC.

Results

A search of the Mayo Clinic electronic health records (October 1993 through March 2016) yielded more than 1325 diagnoses of MDS by central hematopathology. Sixty-four patients fit the criteria for MDS with del(5q) (Table 1). Median age was 72.5 years (range, 38–87 years); 60% were females and 40% were males. Baseline hemoglobin at diagnosis was 9.5 g/dL; all patients had less than 5% bone marrow blasts. Thirty-eight percent of the patients ($n = 24$) were treated with lenalidomide, and 21% ($n = 5$) received concurrent ESA. Of those, 80% ($n = 4$) were receiving epoetin and 20% ($n = 1$) were receiving darbepoetin. Median duration of lenalidomide therapy was 10.5 months (range, 1–44 months). From the entire MDS 5q cohort, 58% of the patients ($n = 37$) received antithrombotic prophylaxis, 76% received aspirin ($n = 28$), 22% ($n = 8$) received anticoagulation with warfarin, and 1 patient was given a direct oral anticoagulant.

The R-IPSS scores for the study cohort were 26% (very low), 62% (low), and 12% (intermediate). Ten percent of patients progressed to AML, with a median time of 41.5 months (range, 10–44 months). Fifty-eight percent ($n = 13$) achieved erythroid hematologic response based on the MDS IWG 2006 criteria [17]; only 22 patients who received lenalidomide had

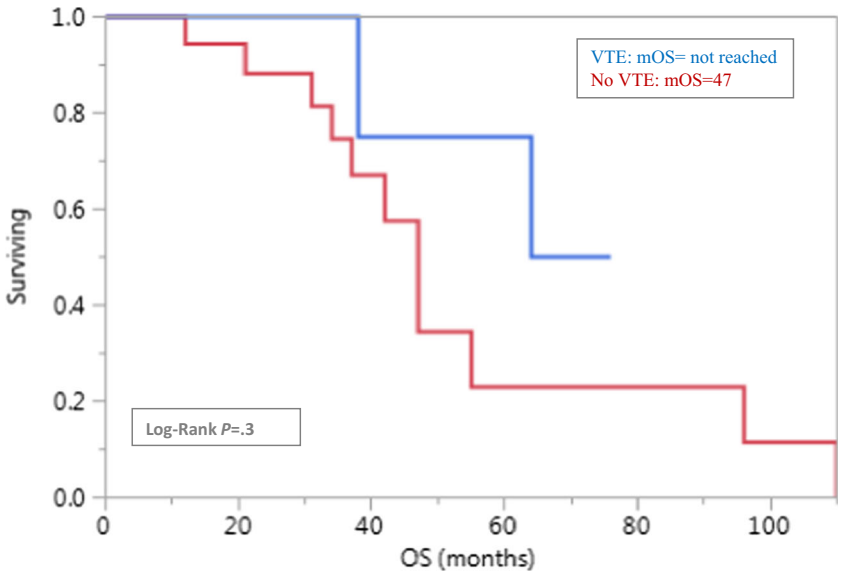

Fig. 2 Overall survival for MDS patients with 5q deletion syndrome ($n = 24$) treated with lenalidomide. mOS indicates median overall survival; OS, overall survival; VTE, venous thromboembolism

follow-up blood counts to assess their response. The median overall survival of all patients in the del(5q) MDS cohort was 4.3 years (ranging from 1 week to 18 years); the diagnosis of VTE during lenalidomide therapy did not statistically affect overall survival on univariate and multivariate analysis (Figs. 1 and 2). Further testing did not show a difference in survival, whether patients were receiving concurrent ESA ($P = 0.530$) or antithrombotic prophylaxis ($P = 0.162$).

The total number of VTE events was 6 (9%) in this cohort, no arterial events were reported. In the lenalidomide-treated group, VTE occurred in 4 patients (17%), all of which were DVTs (Table 2). Pulmonary emboli occurred in the non-lenalidomide-treated group ($n = 2$), and one of these patients had a DVT simultaneously with a PE; there was no statistical difference in the VTE rate between the lenalidomide and non-lenalidomide-treated groups ($P = 0.2$), Table 2 highlights the differences between these two groups. All VTE events occurred after 12 months of lenalidomide therapy (Table 2). One of the 4 patients on lenalidomide therapy who developed VTE was taking antithrombotic prophylaxis.

The median time from starting lenalidomide to development of VTE was 17.6 months (range, 13.8–30.7 months). There was no statistical association between VTE development and blood count at the time of MDS diagnosis (hemoglobin, WBC, and platelets) or the time of starting lenalidomide.

Occurrence of VTE did not affect overall survival of this group; median overall survival for patients who developed VTE was 69 months, versus 48 months in patients without VTE ($P = 0.9$). Only 1 patient from the VTE group progressed to AML.

A total of 4 patients developed VTE during lenalidomide therapy (Table 3). Two were taking warfarin for atrial fibrillation, which was discontinued in both patients for a contraindication for anticoagulation. Lenalidomide was started without considering antithrombotic prophylaxis. The third patient's

Table 2 Comparison between lenalidomide- and non-lenalidomide-treated patients

	Lenalidomide patients	Non-lenalidomide patients	*P* value
Number of patients, no. (%)	24 (37)	40 (63)	
Age, median, year	69	75	0.007
Sex, %			0.3
Male	50	35	
Female	50	65	
CBC at diagnosis, median			
Hemoglobin (g/dL)	9.6	9.7	0.5
WBC (×109/L)	4.6	4.4	0.7
ANC (×109/L)	2417	1917	0.4
Platelets (×109/L)	154	203	0.7
Bone marrow blast, median	2	1	0.07
R-IPSS cytogenetics, %			1
Good	96	97	
Intermediate	4	3	
R-IPSS group, %			0.1
Very low	21	30	
Low	58	65	
Intermediate	21	5	
Transformation to AML, %	17	5	0.2
Time to AML, median, months	37	80	0.2
Median OS, months	38	32	0.5
Patients on antithrombotic prophylaxis, no. (%)	14 (58)	23 (57.5)	1
Antiplatelet	12 (50)	16 (40)	
Anticoagulation	2 (8)	6 (15)	
DOAC	0 (0)	1 (2.5)	
VTE, no. (%)	4 (17)	2 (5)*	0.2
PE	0 (0)	2 (5)	0.5
DVT	4 (17)	1 (2.5)	0.06

*One patient with PE and DVT simultaneously

ANC, absolute neutrophilic count; *R-IPSS*, Revised International Prognostic Scoring System; *DOAC*, direct oral anticoagulant; *VTE*, venous thromboembolism; *PE*, pulmonary embolism; *DVT*, deep vein thrombosis

Table 3 Lenalidomide-only treated MDS patients ($N = 24$)

	VTE	No VTE	*P* value
Patients, no. (%)	4 (17)	20 (83)	
DVT, no. (%)	4 (100)	0 (0)	
PE, no. (%)	0 (0)	0 (0)	
Lenalidomide duration, months (range)	28 (15–44)	9 (1–39)	.055
Lenalidomide ≥ 1 year, no. (%)	4 (100)	0 (0)	.023
Concurrent ESA, no. (%)	1(20)	4 (80)	.496
Antithrombotic prophylaxis, no. (%)	1 (20)	13 (65)	.137
Aspirin	0	12	
Warfarin	1	1	
DOAC	0	0	
Median overall survival, months	Not reached	47	.274
HI-E, no. (%)	4 (100)	9 (50)*	.065

*Data not available for 2 patients

DOAC, direct oral anticoagulant; *HI-E*, hematological improvement–erythroid; *ESA*, erythropoietin-stimulating agent; *DVT*, deep vein thrombosis; *PE*, pulmonary embolism

VTE was felt to be unprovoked and occurred at the age of 73. Lastly, the fourth patient had preexisting superficial thrombophlebitis, and developed acute VTE while taking warfarin. Table 4 highlights the characteristics of those patients and their risk factors to develop VTE.

Discussion

Therapeutic options for MDS are influenced by age, MDS risk category, and comorbid conditions. Intensive chemotherapy and allogeneic stem cell transplantation are considered only for patients who are younger or more fit, with no or limited comorbidities. Since MDS is considered a disease of the elderly, management guidelines should consider tolerability, adverse event profile, and quality of life as factors when choosing medical interventions. Thus, adding lenalidomide to the treatment regimen for MDS in patients either with or without 5q deletion [18] carries the advantage of decreasing red blood cell transfusion requirements, which has its own set of risks (e.g., iron overload, transfusion reactions, infection transmission). On the other hand, lenalidomide is also known to cause myelosuppression, thrombocytopenia, and an increase in the risk of thromboembolism [2]. The American Society of Clinical Oncology considers patients receiving lenalidomide at high risk for thrombosis and recommends prophylaxis [19]. The current National Comprehensive Cancer Network (NCCN) guidelines recommend aspirin with immunomodulator-based therapy for MM to decrease the risk of venous thromboembolism [20]. However, there are no recommendations from the NCCN regarding VTE prophylaxis during lenalidomide therapy in MDS.

Both ESAs and lenalidomide have produced an erythroid response in low- and intermediate-risk MDS [12, 21]; however, the use of ESAs has been associated with increased risk of vascular events in patients with renal disease, which led to a US boxed warning by the FDA [22].

One of the initial reports regarding VTE and lenalidomide use in MDS was presented at the American Society of Clinical Oncology (ASCO) 2008 [23], and that indicated a cumulative incidence for the first VTE of 3.4% in the first 12 months. Postmarketing surveillance in the first 2 years of commercial use of lenalidomide suggested an increased risk of VTE when combined with an ESA, but not when used alone [24]. However, previous studies have not shown an increased risk

Table 4 Characteristics of patient-related risk factors for VTE development during lenalidomide therapy

Patient	Pt #1	Pt #2	Pt #3	Pt #4
Lenalidomide therapy > 12 months	✓	✓	✓	✓
Current diagnosis of VTE	✓	✓	✓	✓
1. Pulmonary embolism	✖	✖	✖	✖
2. Lower extremity DVT	✓	✓	✓	✓
History of prior VTE (DVT or PE)	✖	✖	✖	✖
History of prior superficial vein thrombosis	✓	✖	✖	✖
Cardiac disease (chronic atrial fibrillation)	✖	✓	✓	✖
Development of VTE during anticoagulation	✓	✖	✖	✖
Development of VTE after discontinuing anticoagulation secondary to contraindication	✖	✓	✓	✖
Unprovoked event (no identified risk factor other than lenalidomide treatment)	✖	✖	✖	✓
Presence of central venous access	✖	✖	✖	✖
Immobility	✖	✖	✖	✖
Estrogen therapy	✖	✖	✖	✖

DVT, deep vein thrombosis; *PE*, pulmonary embolism; *Pt*, patient

when treating low- and intermediate-risk group MDS patients with ESA alone [25].

In our single-institution study, we investigated MDS with del(5q), including baseline characteristics, cytogenetic profile, baseline hematologic parameter, and therapeutic interventions, including lenalidomide and ESAs. These data included patients before the FDA approval of lenalidomide and also patients with 5q deletion as the only cytogenetic abnormality based on the WHO 2008 classification (39% [$n = 25$] from the total cohort).

Guidelines for the use of lenalidomide with ESAs have not yet been established, as their combined use is still being investigated in clinical trials. We therefore had a limited number of patients from which to calculate the incidence of VTE and to describe our cohort characteristics. Overall survival was 4.3 years, which falls into a similar category of the low- and intermediate-risk R-IPSS described in the literature (5.3 and 3 years, respectively) [26].

Host factors other than the myeloid neoplasm and its treatments also play an essential role in increasing the risk of venous thromboembolism (e.g., age and comorbid conditions that limit mobility) [27]. Yang et al. [24] described a similar cohort in which the risk of VTE was low in MDS patients treated with lenalidomide, and suggested that the use of antithrombotic prophylaxis is to be based on recognizing additional risk factors. The rate of antithrombotic prophylaxis in the lenalidomide-treated group was 58% ($n = 14$). Additionally, the presence of thrombocytopenia during antithrombotic prophylaxis increased the risk of bleeding and morbidity. In our cohort, the median platelet count at baseline and at hematologic response was 190,000/mm^3 and 127,000/mm^3, respectively.

One observation from this cohort regarding the trend of antithrombotic prophylaxis use is that all patients who were on anticoagulation with warfarin or a novel oral anticoagulant had an indication for long-term anticoagulation (atrial fibrillation, history of VTE prior to MDS, or antiphospholipid syndrome). In this setting, we see a trend from the prescribing physicians to choose antiplatelet agents rather than anticoagulation following the multiple myeloma recommendation, unless the diagnosis of coronary artery disease (CAD) was established before the diagnosis of MDS, in which case the patients were already on antiplatelet agents as secondary prevention treatment for CAD.

Our observation for thrombosis in MDS who did respond lenalidomide beyond 1 year is not similar to the MM literature. When starting induction therapy that includes lenalidomide in the frontline or in relapsed sitting for MM, it was observed that the highest risk of thrombosis occurs in the first 3–6 cycles [28]. Another study demonstrated that thalidomide and its derivatives had an increased hazard of VTE in the first 3 months (HR = 1.4, CI 1.1–1.38) [29].

There are limitations of this single-center retrospective analysis, including the low number of VTE cases and the relatively small size of the MDS with del(5q) cohort which will add difficulty to make clear conclusions. It is also important to mention that the study included patients who were diagnosed and treated before the WHO revision for myeloid neoplasms and before the FDA approval for the use of lenalidomide.

Conclusion

Lenalidomide therapy for MDS with del(5q) is effective in decreasing transfusion requirements and disease progression but carries a risk of VTE. Therefore, when using lenalidomide, an individualized approach to examining risk factors might be warranted. A stronger recommendation for VTE prophylaxis may be needed in MDS patients who undergo lenalidomide therapy.

Author contribution All authors contributed equally to the manuscript.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent This is a retrospective study, approved by the Mayo Clinic IRB; informed consent was obtained from all individual participants included in the study.

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