A MULTICENTER REAL-LIFE STUDY ON ANTICOAGULANT TREATMENT WITH DIRECT ORAL ANTICOAGULANTS IN PATIENTS WITH PH NEGATIVE MYELOPROLIFERATIVE NEOPLASMS

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Key words: myeloproliferative neoplasm; direct oral anticoagulants; venous thromboembolism; atrial fibrillation.

Running title: DOACs in MPNs patients

This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ajh.25990

To the Editor

Patients with Ph-negative (Ph-neg) myeloproliferative neoplasms (MPNs) are at increased risk of thrombotic events. Despite the significant increase in knowledge of pathogenesis, risk stratification and effective biologic treatments of Ph-neg MPNs, arterial thrombosis and venous thromboembolism (VTE) (in particular atypical site VTE) are the main reasons of morbidity and mortality in patients with MPNs [1]. Due to the morbidity and mortality of these complications, antiplatelet and/or anticoagulant agents are commonly administered as primary and/or secondary prophylaxis [2]. In Ph-neg MPNs patients, vitamin K antagonists (VKAs) provide a high level of protection against VTE recurrences, although reported rates of both recurrent thrombosis and major bleeding remain higher compared to the general population [3]. The direct oral anticoagulants (DOACs) dabigatran, rivaroxaban, apixaban, and edoxaban are currently approved for the treatment and/or secondary prophylaxis of VTE and ischemic stroke prevention in atrial fibrillation (AF) in the general population [4]. In cancer patients, recent prospective clinical trials compared edoxaban, rivaroxaban and apixaban versus low-molecular-weight heparin (LMWH) demonstrating the non-inferiority of DOACs, but unfortunately only 10% of enrolled patients were affected by hematological malignancies. Although data on DOACs efficacy and safety in Ph-negative MPNs patients are yet limited [5], DOACs may represent a valuable alternative, given the reduced bleeding risk and low incidence of VTE recurrences and/or stroke. In MPN patients, indication to cytoreductive treatment derived from guidelines suggested to start treatment only in high-risk patients. However, no evidences of the benefits of cytoreductive treatments in preventing recurrent thrombosis after MPN-related atypical site venous thrombosis (i.p. splanchnic vein thrombosis, SVT) have been reported so far. Thus, in general, a life-long anticoagulant treatment is suggested after a first VTE episode within the course of MPN. We report our experience on the administration of DOACs in a real-world setting of Ph-neg MPNs patients affected by VTE or AF. We evaluated

consecutive Ph-negative MPN patients who started DOACs from 2014 to 2019 for VTE or non-valvular AF. Patients were followed at 3 Italian Hematologic centers: University Hospital “Sapienza” in Rome, University Hospital "Paolo Giaccone" in Palermo and “S.M. Goretti” Hospital in Latina. We included patients with a diagnosis of polycythemia vera (PV), essential thrombocythemia (ET), primary or secondary myelofibrosis (MF) and MPNs-unclassified (MPN-U). All MPN patients received a baseline prognostic stratification: PV patients according to cardiovascular risk factors, MF patients according to the international prognostic scoring system (IPSS) and ET patients were stratified according to the international prognostic score for thrombosis in ET (IPSET). The DOACs were started as front line anticoagulant treatment or after a previous treatment with VKA and the dosage was administered according to VTE and AF guidelines and adjusted for liver and kidney function or body weight. DOAC treatment was maintained all over the study and none of the patients changed the type of drug or dosage. For this study we evaluated DOACs safety and efficacy: as regards the safety, we recorded the bleeding events defined according to the International Society of Thrombosis and Hemostasis (ISTH) as major, minor and clinically relevant non-major (CRNM). DOACs efficacy was evaluated in terms of recurrences of thromboembolic events: in the presence of specific symptoms, thromboembolic events were evaluated with recommended imaging techniques (computed tomography, Doppler ultrasound). Since the DOACs start, the patients were checked every 3 months for blood count, renal and liver function. We considered also the baseline comorbidities, in particular the concomitant presence of hypertension, renal failure, diabetes, cardiopathies, previous cancer, neurological diseases and chronic pulmonary diseases. All data were recorded in a dedicated database, including patients’ characteristics, comorbidities, concomitant medication, thrombotic and hemorrhagic adverse events. Patients signed informed consent to the therapy and to the use of medical information for scientific purposes. Data were expressed as mean ± standard deviation (normally distributed data), median and interquartile range (IR) (non- normally distributed data), or as percentage frequencies. Seventy-one patients were enrolled in the study. The patients’ characteristics are reported in table 1. Administered DOACs were: rivaroxaban in 26 (37%) cases, apixaban in 21 (29%), edoxaban in 14 (20%) and dabigatran in 10 (14%). Forty-six out of 71 patients started DOACs as frontline anticoagulant treatment (15 patients were already on

DOACs therapy before MPN diagnosis); 25/71 patients were shifted from a previous VKA treatment. The main reasons for a switch from VKA to DOACs were: instability of the INR (TTR <70%) in 12 patients; adverse events (hypersensitivity with cutaneous rush) related to therapy in 4 patients; difficulties in carrying out regular monitoring check in 9 patients. Thirty-five patients were affected by non-valvular AF: at MPN diagnosis, 10 patients started antiplatelet treatment as primary prophylaxis. In 20 cases, DOACs were started as frontline anticoagulant treatment (8/20 patients were already on DOACs before MPN diagnosis); in 15 patients DOACs were shifted from a previous VKA therapy with a median time of VKA length of 32 months (range 11-92 months). The median follow-up duration of DOACs was 12 months (range 8.7-26).We did not record thrombotic complications, major or CRNM bleeding. One minor bleeding (epistaxis in a ET patient), not requiring DOAC discontinuation because of a spontaneous resolution, occurred. Thirty-six patients presented VTE: 26/36 were of typical sites and 10/36 of atypical sites (including splanchnic venous thrombosis and cerebral sinus vein thrombosis). At MPN diagnosis, 4 patients started antiplatelet treatment for concomitant cardiopathy. In 26 cases, DOACs were started as frontline anticoagulant treatment (7/26 patients were already on DOACs before MPN diagnosis); in 10 patients, DOACs were shifted from a previous VKA therapy with a median time of VKA length of 12 months (range 9-63). The median follow-up duration of DOACs was 15 months (range 12-30.7). Three patients presented a mild thrombocytopenia with platelet count ranging from 80 x 10^9/L to 100x10^9/L at DOACs start. We did not record thrombotic complications during DOACs therapy in VTE population. One patient with MF discontinued DOACs for thrombocytopenia <50x10^9/L. In the 10 patients, previously treated with VKA, 6 thrombotic events were observed during VKAs therapy: 4 recurrences of splanchnic vein thrombosis in 3 patients with primary MF and 1 with PV (all the patients were on cytoreductive therapy and 1/4 patients presented mild thrombocytopenia with a platelet count of 80x10^9/l at the VTE recurrence); 2 deep vein thrombosis in 2 patients with ET (not in cytoreductive therapy and with a platelet count >500x10^9/L). All these patients presented at least 2 comorbidities. During DOACs administration, no major or CRNM bleedings were reported. During VKAs, 1 CRNM bleeding was reported: an intramuscular hematoma of the femoral quadriceps in a MF patient with VTE and no comorbidities. There are growing evidences supporting the use of DOACs for cancer

associated VTE, especially in patients with solid tumors, but the best anticoagulant treatment in MPN patients with highly thrombogenic features is still a matter of discussion [6]. In our real-life setting, DOACs resulted safe and effective. Furthermore, considering that the majority of our patients presented at least 2 comorbidities (29 patients presented ≥ 2 comorbidities) and 10 patients presented VTE in atypical sites, DOACs seem a suitable option also for frail MPN subjects at increased thrombotic risk. Finally, 11 patients were treated with the JAK2 inhibitor ruxolitinib: the association seemed safe and effective even in this combination, suggesting that co-administration of DOACs and ruxolitinib is feasible. In conclusions, our results proved that in Ph-negative MPNs patients, anticoagulant treatment with DOACs is well tolerated, apparently safe, without recurrences of thrombotic events and significant bleeding complications even in high risk patients. Although the limitations due to the retrospective nature, these data are in line with the currently limited literature so far reported. Under the perspective of a long-term anticoagulant treatment during MPNs, DOACs seem a feasible option even in second line. A prospective clinical trial is required to confirm these findings.

Disclosure: none.

Funding: none

Data Availability Statement: all the data are deposited in specific database. The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Figure and Table

Table 1. Patients'characteristics

	AF	**VTE**
71 patients	35	36
Age at MPN diagnosis (median)	72 (67-79)	67 (65-77)
Age at DOACs start (median)	74 (67-79)	70 (65-77)
MPN Type		
PV	10	15
ET	13	15
MF	9	4
MPN-U	3	2
Risk stratification		
PV low	3	2
High	7	13
ET (IPSET)		
Low	2	2
Intermediate	2	5
High	9	8
MF (IPSS)		
Low	2	0
Intermediate -1	4	2
Intermediate -2	3	2
High	0	0
Driver mutation		
JAK2V617F	26	28
CALR	2	0
MPL	1	1
Negative	6	7

MPN treatment		
Hydroxycarbamide	20	30
Ruxolitinib	8	3
6-mercaptopurine	1	0
Interpheron-alpha	1	0
Anagrelide	0	1
Phlebotomy	1	0
Observation	4	2
Comorbidities		
Hypertension	18	14
Cardiopathy and arrhythmias	10	7
Diabetes	6	2
Renal impairment	1	3
Respiratory disease	2	2
History of neoplasm	0	4
No comorbidities	13	9
1 comorbidity	10	9
2 comorbidities	7	7
3 comorbidities	3	10
4 comorbidities	1	1
5 comorbidities	1	0

AF = atrial fibrillation; VTE = venous thromboembolism; PV = polycythemia vera; ET = essential thrombocythemia; MF = myelofibrosis; MPN-U = myeloproliferative neoplasm-unclassified; IPSET = international prognostic score for thrombosis in ET; IPSS = international prognostic scoring system