COVID-19 IN PATIENTS WITH MYELOPROLIFERATIVE NEOPLASMS: THE RISK OF THROMBOEMBOLIC EVENTS AND CURRENT OPTIONS FOR ANTITHROMBOTIC PROPHYLAXIS

O. M. Kostiukevych[1], L. K. Benkovska[1], A. M. Kravchenko[1], T. Ya. Chursina[2], K. O. Mikhaliev[1]

[1] State Institution of Science «Research and Practical Center of Preventive and Clinical Medicine» State Administrative Department, Kyiv, Ukraine
[2] Bukovinian State Medical University, Chernivtsi, Ukraine

Summary

Aim: to provide a literature review of the presently available data on the risk of thromboembolic events and current options for antithrombotic prophylaxis in patients with myeloproliferative neoplasms (MPN) patients with concomitant coronavirus disease 2019 (COVID-19).

Material and methods. The thematic scientific papers, published predominantly during the last decade (including the references regarding SARS-CoV-2 infection (COVID-19) of the last three years), constituted the study material. The research methodology involved bibliosemantic method and structural and logical analysis.

Results and discussion. MPN and SARS-CoV-2 infection (COVID-19) are both conditions with inherently enhanced susceptibility to thromboembolic events (venous and arterial). Along with the specific pathophysiological pathways, MPN and COVID-19, in case of their constellation, share overlapping pathomechanisms of hypercoagulability. As of today, the antithrombotic prophylaxis in MPN/COVID-19 patients (primary and secondary) is carried out according to the guidelines and algorithms, including those regarding general principles of the use of anticoagulants (oral or parenteral) and antiplatelet agents, and those specifically addressed to MPN or SARS-CoV-2 infection. These documents are constantly updating as the results of ongoing trials become available. Considering the relatively low prevalence of MPN, and the absence of specific guidelines, devoted to MPN in tandem with SARS-CoV-2 infection, the conduction of global registry studies is of crucial importance, aiming to provide a continuous and thorough collection and analysis of the data, related to the characteristics of this particular patients' population, pathological background and clinical features of thromboembolic complications, as well as short- and long-term outcomes.

Conclusion. The comprehensive study of basic, epidemiological and clinical data regarding various aspects of thrombosis/thromboembolism in case of MPN/COVID-19 constellation, is a multidisciplinary task, which should be performed with an ultimate goal to improve already implemented and develop novel approaches to antithrombotic management of such patients.

Key words: **SARS-CoV-2 infection, coronavirus disease 2019 (COVID-19), myeloproliferative neoplasms, thrombosis, antithrombotic prophylaxis, antithrombotic therapy**

INTRODUCTION

The World Health Organization on March 11, 2020, has declared a pandemic of coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1]. COVID-19 is associated with a high prevalence of coagulopathy and thrombosis, as well as occlusions in the microcirculation, leading to severe morbidity and mortality [2, 3]. Thromboembolic complications (venous thromboembolism (VTE) and/or arterial thrombosis) has been recognized as a major concern in the certain categories of COVID-19 patients, such as those with common cardiovascular risk factors (including hypertension, obesity and diabetes), cardiovascular and respiratory diseases, and cancer. Patients with myeloproliferative neoplasms (MPN), being inherently

prone to develop thromboembolic complications, are thought to be extremely vulnerable to these events [2, 4].

Philadelphia (BCR-ABL1)-negative MPN, including polycythemia vera (PV), essential thrombocythemia (ET), (primary) myelofibrosis (MF) and prefibrotic MF (pre-MF), are characterized by a predisposition to thrombosis, which is a consequence of both quantitative and qualitative abnormalities in myeloid blood cells [3, 5]. Patients with MPN demonstrate a 2-4 higher incidence of thrombotic complications, than in general population [2, 5], and carry a 3- and 10-fold higher risk of arterial and venous thrombosis, respectively, as compared to controls [6]. They are also characterized by a high risk of spontaneous or drug-related bleeding [7], being of crucial importance when considering to start the antithrombotic prophylaxis and therapy.

Although the available data on thromboembolic events in patients with concomitant MPN and SARS-CoV-2 infection are scarce, one may assume the susceptibility to develop thrombotic complications to be more pronounced in patients with MPN, suffered from COVID-19 [2, 5]. Therefore, an accumulating of evidence regarding the epidemiological aspects of thromboembolic complications in MPN/COVID-19 constellation, along with a deepening of understanding the associated risk factors and principal pathomechanisms of related hypercoagulability, could be of great benefit in improving and individualizing the antithrombotic prophylaxis and therapy in such patients.

AIM

This paper aims to provide a literature review of the presently available data on the risk of thromboembolic events and current options for antithrombotic prophylaxis in MPN patients with concomitant COVID-19.

MATERIAL AND METHODS

The thematic scientific papers, published predominantly during the last decade (including the references regarding SARS-CoV-2 infection (COVID-19) of the last three years), constituted the study material. The literature search was conducted by the use of Google Web Search and PubMed search engines by the following keywords: SARS-CoV-2 infection, coronavirus disease 2019 (COVID-19), myeloproliferative neoplasms, thrombosis, antithrombotic prophylaxis, antithrombotic therapy, as well as their combinations. The research methodology involved bibliosemantic method and structural and logical analysis.

REVIEW AND DISCUSSION

Risk factors and principal overlapping pathomechanisms of hypercoagulability in patients with MPN and COVID-19. Up-to-date, the number of clinical and biological risk factors, contributing to the increased risk of thrombosis in MPN and COVID-19, have been proposed. In patients with MPN, clinical risk factors, including older age (>60 years), history of thrombosis and cardiovascular risk factors, are currently used for thrombosis risk stratification and to guide clinicians with the choice of thromboprophylaxis modality. Additionally, the biological risk factors for thrombosis in MPN patients should also be considered, particularly the JAK2 V617F mutation, leukocytosis, high hematocrit, genetic thrombophilia and the increased level of C-reactive protein.

Among the risk factors, being common to both MPN and COVID-19, one should note the aging, data on previous thrombosis and the presence of cardiovascular risk factors (i.e., arterial hypertension, type 2 diabetes, obesity, smoking and chronic kidney failure) and conditions (in particular, coronary heart disease and atrial fibrillation [AF]). At the same time, there are specific factors, associated with the increased thrombotic risk in COVID-19 patients, such as the presence of comorbidities (moderate/severe asthma, preexisting chronic obstructive pulmonary disease, pulmonary fibrosis, cystic fibrosis and chronic liver disease), as well as the factors, related to disease severity and inherent to hospitalized patients (sepsis, pneumonia, immobilization, hypoxia, longer interval from symptoms onset to admission, acute respiratory distress syndrome, mechanical ventilation, and the use of central venous catheters). Finally, the abovementioned leukocytosis and the increased C-reactive protein level, and other parameters, including D-dimer, chest computed tomography scoring and various blood cell count ratios, — all were proposed as biological risk factors for stratifying the thrombotic risk in COVID-19 patients [5].

MPN and COVID-19 have both specific and common pathomechanisms of hypercoagulability. With respect to MPN, the platelets, erythrocytes and leukocytes, stemming from the clonal proliferation of JAK2-mutated hematopoietic progenitor cells, are constitutively activated, and serve as triggers of clotting formation [8]. In its turn, the long-term (chronic) (sub)inflammatory mechanisms, caused by the abnormal and clonal proliferation of JAK2-mutated myeloid cells, are highly involved in the development of MPN-related systemic hypercoagulability, contributing to the overexpression of adhesion molecules by blood cells and endothelial cells, and, as a result, favoring cellular interplays and thrombosis. Additionally, in MPN patients, JAK2 V617F mutation has been detected in mature endothelial cells, carrying the increased prothrombotic ability due to P-selectin overexpression [9]. Finally, the blood hyperviscosity should also be considered among the specific mechanisms of hypercoagulable state in MPN patients [5].

The principal pathomechanisms of COVID-19-associated coagulopathy are being actively investigated [3]. In COVID-19, the acute SARS-CoV-2 infection acts on the prothrombotic characteristics of various hemostatic compartments [5]. Among the possible mechanisms of the systemic damage of macro- and microcirculation, one

may consider that SARS-CoV-2 affects the human body through the angiotensin-converting enzyme 2 receptors, being distributed over the vessel bed in various organs and tissues [2]. The viral infection serves as a trigger of thrombo-inflammation, being a crucial pathomechanism for thrombus formation [5]. The major features of systemic thrombo-inflammation process include hemostatic abnormalities (i.e., elevation of D-dimer and fibrinogen), dysregulated immune response, along with endothelial activation, dysfunction and damage [10, 11]. A maladaptive (excessive, hyperactive) innate immune systems response, named the «cytokine storm», along with hypoxia, endothelial damage and complement cascade activation, are involved [12, 13], and precipitate the occurrence of thrombosis. Besides, it has been demonstrated the neutrophil extracellular trap formation (NETosis) to be linked to COVID-19-related thrombosis [14].

The available evidence on the risk of thromboembolic complications in patients with MPN [2, 15] may reflect the links between MPN and COVID-19 in terms of thrombosis. Among the overlapping MPN/COVID-19 pathomechanisms of hypercoagulability, the following ones should be highlighted, particularly the proinflammatory state, platelet activation, neutrophil activation and NETosis, endothelium activation, dysfunction and damage, the action of cell adhesion molecules and hypoxia [3, 5, 15]. Additionally, the MPN phenotype could be one of the factors, partially contributing to the increased risk of thrombosis in patients with COVID-19 [2].

Currently available evidence on thromboembolic complications in MPN patients, suffered from COVID-19: results from the certain studies. Based on the evidence regarding the higher risk of thromboembolic complications in both MPN and COVID-19, and given that relatively low prevalence of MPN, the MPN-COVID study has been launched [2], being an international, multicenter, retrospective cohort study collecting data in 162 MPN patients, namely ET (n=48), PV (n=42), pre-MF (n=16) and MF [n=56]), hospitalized in 38 specialized hematology European centers, during the first wave of COVID-19 pandemic. The primary outcome was the incidence of pulmonary embolism (PE), with or without deep vein thrombosis (DVT) of the legs. Secondary outcomes were the occurrence of any other major thrombosis (including myocardial infarction, stroke and peripheral arterial thrombosis), major bleeding and death. The primary goal of this retrospective observational study was to evaluate the incidence of thrombosis and bleeding and to identify associated predictors [2].

The study revealed that cumulative rate of arterial and VTE events was 8,6%, occurring in 14 of 162 MPN patients during 60 days of observation for COVID-19. Totally, 15 thrombotic events were registered in patients, managed at home, hospitalized in regular wards or intensive care units (ICU), with the majority of VTE ones (n=12

[7,4%]), corresponding to previously reported data [16, 17], and indicating, that the occurrence of these thrombotic complications was more closely related to COVID-19 rather than MPN, in which events were more commonly represented by arterial thrombosis [6, 7, 18]. Correspondingly, the rest three (1,9%) arterial thrombosis cases included myocardial infarction, stroke and peripheral arterial thrombosis (one case per condition). It is worth noting, that 11 of 12 VTE cases were PE (including one case being concomitant with DVT).

Considering the MPN phenotype, the rate of VTE in PV and MF was 4,8% (2 of 42) and 3,6% (2 of 56), respectively, being similar to that observed in non-MPN acutely ill COVID-19 patients, hospitalized to regular wards [19]. On the contrary, the ET group was characterized by the higher rate of VTE (8 of 48 [16,7%]), even despite the absence of significant difference in COVID-19 severity parameters as compared to other MPN phenotypes, and regardless of the level of inflammation markers. The majority of VTE events, detected in ET patients, were PE (7 of 8 cases, including one PE/DVT concomitant case). Of note, in ET patients the vascular events happened shortly after hospital admission and reached the reported rate after 30 days of observation. In addition, the observed in [2] incidence appeared to be higher than that revealed in most series of non-MPN patients with COVID-19, hospitalized to regular wards [19].

Discussing the higher frequency of VTE, as compared to arterial thrombotic events, T. Barbui et al. [2] point out that this finding seems to be strictly linked to COVID-19 itself, in contrast to the settings outside SARS-CoV-2 infection, where one could observe the opposite rules [6, 7, 18]. As anticipated, the study [2] revealed a significantly higher incidence of thrombosis in ICU patients, in comparison to those requiring non-invasive respiratory support and admitted to regular wards. Notably, patients with thrombosis demonstrated around 25% lower survival as compared to those without such complications [2].

Thus, T. Barbui et al. demonstrated the ET to carry the highest risk of VTE among patients with MPN [2], triggering the clinicians to consider the possibility of thromboembolic events in ET patients, suffering from COVID-19. Importantly, the association between ET and thrombosis, regardless of inflammation markers and the severity of COVID-19, is an intriguing finding, which could be usefully explored in further research, involving the larger series of patients. At the same time, such data emphasize the role of platelets in the thrombogenesis in MPN patients with COVID-19 [2].

Along with the risk of VTE, patients with MPN and COVID-19, as mentioned above, have increased rates of arterial thrombosis [5]. The study by O. Leiva et al. [15] demonstrated, that MPN patients with COVID-19, as compared to SARS-CoV-2 positive patients without MPN, carry the higher risk of arterial thrombosis (included the

cases of myocardial infarction, ischemic stroke or transient ischemic attack; systemic embolism; and major adverse limb events), despite more frequent use of anticoagulation and aspirin before COVID-19 diagnosis, and, importantly, regardless the high rates of pre-COVID cytoreductive therapy (77% of MPN patients), which is routinely used in such cases with the purpose to reduce of the risk of thrombosis.

It should be noted, that in patients with and without MPN, enrolled in [15], most thrombotic events occurred within the first month (30 days) of COVID-19 diagnosis, corresponding with previous evidence [20]. Considering the well-known long-term risk of arterial thrombosis in MPN patients, being the highest within 3 months of MPN diagnosis and diminishing thereafter [6], the findings from [15] of possibly increased short-term risk of arterial thrombotic complications in patients with MPN and concomitant COVID-19 are likely to be of practical importance. Nevertheless, O. Leiva et al. [15] acknowledge the small number of events in either group (MPN vs. no-MPN), and highlight the need of further larger studies to confirm the obtained results, particularly to establish the long-term effects of COVID-19 in patients with MPN, including the risk of thromboembolic complications.

Particular clinical and pathophysiological considerations regarding the available evidence on thromboembolic events in patients with MPN, infected by SARS-CoV-2. The classic venous and arterial thrombotic complications represent only a part of the vascular problem in COVID-19 patients. In particular, the autopsy findings consistently documented the widespread microvascular thrombosis and extensive pulmonary angiogenesis [21, 22], allowing to propose the concept of «in situ» pulmonary thrombosis [23, 24]. Additionally, the frequent extrapulmonary micro-thrombosis and thromboemboli (including heart and kidneys) have been also detected, which was consistent with disease-specific hypercoagulability [21], and leading to rapid respiratory deterioration, multiorgan failure (MOF) and eventually death [25, 26].

In the MPN-COVID study, T. Barbui et al. [2] reported that fatal events were in 41 of 162 patients (25,3%), with pneumonia (n = 15; 37%) and MOF (n = 17; 41%) being the most frequent ones (remaining 9 cases (22%) were of unknown or unspecified causes). Of note, among the 11 deaths that occurred in ET patients, pneumonia was more frequent (n = 6; 55%) than in PV (n = 2/6; 33%) and MF (n = 6/21; 29%), while the fatalities from MOF did not differ in ET (n = 5/11; 45%) and PV (n = 3/6; 50%). Considering the significantly higher thrombosis rate in ET, associated, as mentioned above, with lower survival, the authors supposed that the detected fatal events might be associated with organ micro-thrombosis. In support of the proposed hypothesis, T. Barbui et al. [2] demonstrated, that, at COVID-19 diagnosis, the enrolled patients had significantly lower total platelet count, as compared to

the value at last follow-up visit before the SARS-CoV-2 infection was diagnosed. The reported total platelet number decline was significant in ET, and less pronounced (but non-significant) in PV patients, being associated with higher mortality rate, mainly due to pneumonia. Besides, the total platelet number decline was also significant in MF patients, but its pre-COVID value was more than twice as lower than that in ET group. Moreover, the at-COVID total platelet count level tended to be lower than pre-COVID one in patients, died of MOF [2].

Among other noteworthy aspects of the MPN-COVID study [2], one should note the D-dimer values, which, as expected, were reported to be significantly higher in ET patients than in those without thrombosis. Importantly, that, among predictors of VTE in hospitalized patients with COVID-19, the elevated D-dimer levels have been associated with coagulation-associated complications, critical illness and death [5]. Finally, according to the multivariable analysis in [2], ET phenotype and elevated neutrophil/lymphocyte ratio were associated with the increased risk of thrombosis.

The findings from [2] suggest that platelets play a significant role in the thrombogenesis in patients with MPN, suffered from COVID-19. The revealed drop in the total platelet count possibly indicates a platelet consumption due to the process of low grade disseminated coagulation, which might be related to the systemic SARS-CoV-2 associated vascular endothelial damage, involving the series of pathomechanisms (particularly the complement activation, as well as the interaction of platelets, leukocytes and neutrophil extracellular traps with endothelium), and, consequently, leading to classic arterial and venous thrombosis, with the vessel occlusion and hypoxia in the lungs and other tissues [5, 10-12, 14, 27]. Of note, the authors [2] suppose, that in, at least, some MPN patients, who died because of sudden respiratory deterioration, the decline of platelet number, associated with the initially diagnosed pneumonia, might be due to pulmonary thrombosis, being related to «local» intravascular coagulation and complement system activation [21-24].

Primary antithrombotic prophylaxis in MPN patients with concomitant COVID-19: the use of parenteral anticoagulants. The potential increased risk of thromboembolic complication in patients with MPN has important clinical implications with regard to antithrombotic prophylaxis by the use of anticoagulants and antiplatelets. As of today, however, there are no specific standards regarding antithrombotic prophylaxis in MPN patients, affected by COVID-19. In particular, the ideal dosing of primary anticoagulant prophylaxis in hospitalized COVID-19 patients is still a matter of debate [4, 15].

According to the American College of Chest Physicians (ACCP) and American Society of Hematology (ASH) guidelines, the prophylactic (low-dose) low

molecular weight heparin (LMWH) or fondaparinux once daily, or unfractionated heparin (UFH) subcutaneously twice or thrice daily, are recommended to all acutely ill hospitalized medical and critical patients, unless there are contraindications, such as active bleeding or high bleeding risk [28, 29]. The specific guidelines from the major scientific societies, devoted to COVID-19 management, suggest thromboprophylaxis with low- or intermediate-dose LMWH after a careful assessment of the bleeding risk (Table) [5].

Table

Guidelines from professional societies on the LMWH dose for primary thromboprophylaxis in critically ill and acutely ill patients with COVID-19 [5]

Society	Critically ill patients	Acutely ill patients	Postdischarge
ACCP [30]	Prophylactic	Prophylactic	None
AC Forum [31]	Intermediate	Prophylactic	None
ASH [32]	Prophylactic	Prophylactic	None
ISTH [33]	Prophylactic or intermediate	Prophylactic	None or prophylactic
SISET [34]	Prophylactic	Prophylactic	None

Note: these guidelines are constantly evolving and updating as the results of ongoing trials become available

Given the current lack of specific evidence on which dose of LMWH has a most favorable risk/efficacy profile in MPN/COVID-19, in practice, the dose could only be chosen on an empirical basis, considering the presence of common vascular risk factors [5].

The aforementioned MPN-COVID study [2] appears to be the only published so far retrospective study on the incidence and risk factors of thrombosis and bleeding in patients with MPN complicated with COVID-19, where LMWH was used as antithrombotic prophylaxis in most cases. Particularly, all but two patients with VTE, registered in [2], received LMWH prophylaxis (10 patients totally; low LMWH doses (4000-6000 IU subcutaneous fixed dose q 24 h) or intermediate doses — 5 patients; and therapeutic LMWH doses (100 IU/kg of body weight subcutaneously q 12 h) — 5 patients; of note, LMWH doses higher than the prophylactic ones, but not reaching those of therapeutic level, were defined as «intermediate dose»). Thus, one should bear in mind the certain heterogeneity of the data regarding thromboprophylaxis with various regimens of LMWH [2].

The number of studies have been investigated the use of low (prophylactic), intermediate (half-therapeutic), and full (therapeutic) doses of anticoagulants (mainly LMWH or UFH) as primary thromboprophylaxis regimens in acutely ill and critically ill COVID-19 patients [5]. Particularly, the evidence regarding the superiority of therapeutic-dose anticoagulation in non-critically ill patients with COVID-19 has been recently presented in [35]. At the same time, the issue on the potential benefit from intermediate-to-therapeutic dosing of thromboprophylaxis in patients with MPN/COVID-19 constellation, regarding the high risk of thromboembolic complications, needs to be further elucidated [15].

On the contrary, according to currently available data, the intermediate- and therapeutic-dose anticoagulation did not demonstrate a mortality benefit in critically ill patients with COVID-19, as compared to low-dose thromboprophylaxis, being associated with the significant increase of bleeding risk and the risk of thrombocytopenia [5, 15, 35-37].

The use of antiplatelets and cytoreductive therapy to reduce the risk of thromboembolic events in MPN patients, including those with concomitant COVID-19. According to recently updated ASH provisions, regarding MPN and COVID-19 [38], all the hospitalized MPN patients with known or suspected SARS-CoV-2 infection, as stated above, should receive the prevention of thromboembolic complications by the use of parenteral anticoagulants. At the same time, in MPN patients without documented COVID-19 or symptoms, given the baseline increased risk of thrombosis, and the real possibility of asymptomatic SARS-CoV-2 infection, the ASH suggests strict adherence to current treatment goals aimed at decreasing the risk of thrombosis, including antiplatelets and cytoreductive therapy [38].

Regarding the use of antiplatelets for the prevention of thrombotic complications in MPN, the use of low-dose aspirin (75-100 mg) once daily as a primary thromboprophylaxis is recommended for low-risk patients with PV. In addition, the aspirin should be considered twice daily in case of inadequate control of microvascular symptoms, the presence of cardiovascular risk factors, and in patients with leukocytosis. In its turn, high-risk PV patients must receive the cytoreductive therapy to minimize the thrombotic risk [5].

The low-dose aspirin as a primary thromboprophylaxis is recommended to use in low- to high-risk ET patients, whereas very low risk patients might not require any therapy, unless the cardiovascular risk factors are presented. Besides, cytoreduction is recommended in patients with intermediate-risk ET and cardiovascular risk factors, as well as in high-risk patients [39].

In patients with MF, the real incidence of thrombotic complications might be obscured by other major competing conditions (i.e., acute leukemia transformation, infections, etc.), therefore, management of such patients is directed

at symptom relief or disease eradication, rather than thromboprophylaxis [5].

However, in patients with pre-MF the following pragmatic approach has been proposed: 1) observation in patients without a history of thrombosis, and without any thrombotic risk factors (in particular, the age >60 years, or cardiovascular risk factors, or *JAK2* mutation, or leukocytosis, or microvascular symptoms); 2) low-dose aspirin in patients without a history of thrombosis, but with thrombotic risk factors; and 3) aspirin or oral anticoagulants in patients having a positive history of arterial or venous thrombosis, respectively, and hydroxyurea as a first-line cytoreduction in case of thrombocytosis or leukocytosis [40].

In general, currently updated ASH's provisions suggest against the adjustment or abruption of MPN therapy in patients, who have developed the COVID-19 infection, except for drug-drug interactions [38]. Particularly, in patients, who start coronavirus-directed medications and are on ruxolitinib, a dose modification of ruxolitinib (downward in particular if on lopinavir/ritonavir) can be considered, but abrupt cessation of ruxolitinib should be avoided, otherwise there is a risk of sudden worsening of the cytokine reaction from MF, as well as from the COVID-19 infection. Cytoreductive therapy (hydroxyurea, anagrelide, interferon) does not need to be empirically adjusted in someone with COVID-19 [38].

In line with this provision, the COVID-19 Treatment Guidelines Panel recommends that patients with COVID-19, who are receiving antiplatelets (or anticoagulants) for underlying conditions, continue these medications unless significant bleeding develops or other contraindications are present (recommendation AIII) [41].

Particularly, in COVID-19 patients with the history arterial thrombosis (transient ischemic attack, ischemic stroke, myocardial infarction or peripheral arterial thrombosis), or with percutaneous coronary intervention (within ≤ 3 months), it is strongly recommended not to discontinue antiplatelet drugs, unless clinical circumstances or hemorrhagic events prevent it. The combined use of aspirin with LMWH could be proposed in hospitalized patients, unless contraindications, occurring during in-hospital stay (acute liver failure, severe renal failure, severe thrombocytopenia, documented drug interactions or planned invasive procedures) [27].

Antithrombotic prophylaxis in patients with MPN, affected by SARS-CoV-2 infection: the examples of clinical scenarios. T. Barbui and V. de Stefano in their recently published review [27] proposed several clinical scenarios regarding the antithrombotic prophylaxis in MPN patients, suffered from COVID-19, considering the history of thrombosis and the level of care (at-home, with the transfer to in-hospital settings) (Fig.).
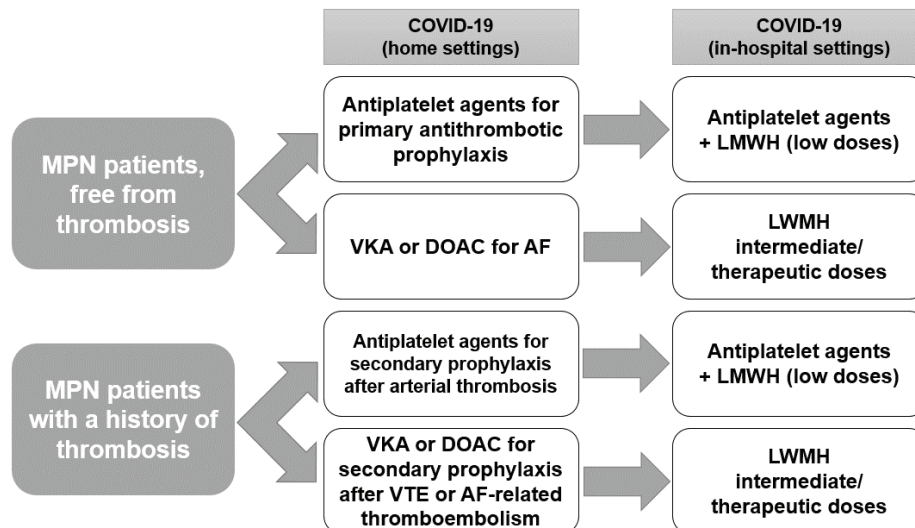

Fig. The certain scenarios (flowcharts) of antithrombotic prophylaxis in patients with MPN and COVID-19 (adapted from [27])

The authors [27] highlight, that in patients with non-severe SARS-CoV-2 infection, the regimen of antithrombotic prophylaxis corresponds to that recommended for non-COVID-19 patients. Contrary, in case of medium-to-high COVID-19 severity, prevention can be modified. For instance, some MPN patients with SARS-CoV-2 infection may require higher doses of heparin.

High-risk MPN patients, namely those with the history of VTE or AF-related thromboembolism, being infected by SARS-CoV-2 infection and receiving a care in home settings, continue to use their oral anticoagulants (either vitamin K antagonists (VKA) or direct oral anticoagulants [DOAC]) for the secondary antithrombotic prophylaxis. The same is related to MPN patients with AF, but free from thromboembolic complications, who continue to use their oral anticoagulant therapy with the aim of primary thrombosis prevention. In case of these two «virtual» patients are hospitalized, the oral anticoagulants

could be switched to intermediate/therapeutic doses of heparin, depending on COVID-19 severity and patient's characteristics.

In some MPN/COVID-19 patients, when their condition allows it, the continuation of VKA or DOAC administration even during the acute phase of SARS-CoV-2 infection might be discussed [27]. Particularly, considering the potential use of DOAC, the report [42] deserves attention, i.e. the data on clinical benefit of apixaban for antithrombotic prophylaxis in patients with COVID-19, demonstrating the mortality decrease without increasing the risk of bleeding. Given the evidence, accumulated to date, including the data on increased risk of ET-associated thrombotic complications, K. Takasaki et al. [4], while discussing their clinical experience, suggest that that apixaban could be useful and safe for antithrombotic prophylaxis in patients with ET suffered from COVID-19. At the same time, considering the relatively small amount of actual data regarding the association of COVID-19 and ET, further investigations are strongly needed to establish the effectiveness and safety of antithrombotic prophylaxis and treatment in such patients [4].

However, considering potential drug-drug interactions of VKA/DOAC with most antiretroviral drugs at the level of liver cytochromes, such as CYP2C9 and CYP3A4, the advice exists for oral anticoagulants to be switched to LMWH prophylaxis.

Notably, T. Barbui and V. de Stefano [27] mention, that the use of intermediate-to-therapeutic doses of heparin can also be considered in ICU patients with ET, presented with a rapid decline of total platelet count and progressive respiratory failure, mainly if the clinical worsening had occurred despite the administration of prophylactic doses of heparin. Importantly, the previously reported higher incidence of ET-related VTE, as compared to PV and primary MF, and higher mortality risk, associated with thrombosis [2], may justify some risks of bleeding [27].

Secondary antithrombotic prophylaxis as a following step after VTE treatment in MPN and MPN/COVID-19 patients. In general, treatment of VTE, including DVT and PE, in patients with MPN [43], correspond with the existing guideline-directed principles elaborated for those without MPN [44-47], and subdivided into an acute (first 5-10 days), long term (from end of acute treatment to 3-6 months) and extended (beyond 3-6 months) phases. It is worth mentioning, that the proposed schemas currently do not differ for patients with MPN, suffered from SARS-CoV-2 infection [5].

The long-term anticoagulation (3-6 months) is aimed at the secondary prevention of VTE (including DVT of the legs and PE), being carried out in patients with MPN to the same principles as in those without MPN [5]. In particular, the continuation of anticoagulant therapy is based on evaluation of the underlying risk factors for VTE

recurrence. Moreover, the long-term and, possibly, extended (after 6 months) use of anticoagulation is recommended in MPN patients owing to the presence of chronic hematologic malignancy itself, being a permanent risk factor for thrombosis. Among other strong predictors for VTE recurrence in MPN patients, one should consider the age older than 60 years and history of thrombosis [5, 44-47].

Concerning the risk of thrombotic complications after COVID-19, the results from the CORE-19 registry recently demonstrated, that postdischarge VTE, arterial thromboembolism and all-cause death occurred frequently after COVID-19 hospitalization. The set of factors, associated with the increased risk of this composite end-point, included advanced age, cardiovascular risk factors, the presence of chronic kidney disease, IMPROVE-DD VTE score ≥4, and intensive care unit stay. Besides, the authors [48] demonstrated, that anticoagulation might reduce that risk by 46%. However, other data [49, 50] suggest that the obtained results in [48] seem to be controversial.

Both VKA or DOAC can be used for the long-term anticoagulant regimen [45-47]. Currently, after acute treatment with LMWH, the early initiation of VKA is the most used option for patients with MPN [5, 45-47].

However, there is a lack of evidence regarding the efficacy and safety of DOAC in patients with MPN, complicated by VTE [5]. The results, obtained from the small series of patients with MPN treated with DOAC have been recently published [51]. Moreover, T. Barbui et al. [52] conducted a large retrospective study of 442 patients with MPN receiving DOAC (factor Xa inhibitors) or VKA either for VTE or AF, and demonstrated a similar risk/benefit profile of both regimens for treatment of VTE in MPN.

In respect of antiplatelets, the evidence on a moderate protection from VTE recurrence by aspirin is available for both non-MPN [45] and MPN patients [53], who discontinue the use of VKA. According to ACCP guidelines, in patients with an unprovoked proximal DVT or PE, who are stopping anticoagulant therapy and do not have a contraindication to aspirin, the aspirin is suggested over no aspirin to prevent recurrent VTE (Grade 2B) (update 2016 [45]).

According to the algorithm of the secondary antithrombotic prophylaxis in MPN patients after VTE [43], the long-term VKA therapy is recommended in patients with unprovoked proximal DVT or PE, as well as for recurrent VTE. In case of distal DVT, the use of VKA is recommended for 3-6 months (unprovoked VTE) or 3 months (provoked VTE), followed by aspirin treatment. In patients with provoked proximal DVT or PE, the use of VKA is recommended for 6-12 months, with the following aspirin treatment. The authors [43] also mention, that the use of DOAC should be discussed on an individual basis, considering the risk of VTE recurrence and bleeding.

Noteworthy, V. de Stefano et al. [43] emphasize the secondary antithrombotic prophylaxis in MPN patients after VTE to be unsatisfactory because of its suboptimal efficacy and safety, justifying the need for multicenter retrospective and prospective trials aiming at improvement of treatment strategies.

The use of antithrombotic therapy in patients with MPN and COVID-19: the cautions related to bleeding risk. Importantly, one should suspect a problem of bleeding, being inherently related to MPN patients, and also regarding the use of antithrombotic therapy [2, 5, 7]. T. Barbui et al. in the MPN-COVID study [2] demonstrated that 7 of 162 (4,3%) patients suffered from major bleeding, in particular those with MF, where all the four hemorrhagic episodes required blood transfusions. The revealed in [2] bleeding incidence is slightly higher than it was estimated that reported (2,3%) in the general population with COVID-19 (2,3%) [54]. The authors [2] highlight, that, while the peak of thrombotic events occurred in the first days after SARS-CoV-2 infection diagnosis, bleeding episodes were reported later, starting 2 weeks afterwards. It should be noted, that in 4 of the 7 cases, coagulopathy (activated partial thromboplastin time prolongation) or total platelet count $<30 \times 10^9$/L was associated with severe bleeding, suggesting the empiric intensification of LMWH to be provided with caution, particularly in patients with MF [2]. Therefore, before the initiation or adjustment of anticoagulation, a scrupulous assessment (and reevaluation) of the bleeding risk factors in both patients with MPN and COVID-19 is required [5].

The abovementioned study [15] revealed the lower rates of in-hospital anticoagulation in patients with MPN, in contrast to the higher frequency of baseline anticoagulation use as compared to patients without MPN in the enrolled cohort. These findings, at least partially, could be explained by increased rates of thrombocytopenia and anemia in patients with MPN, as compared to the alternative group. In addition, considering the increased risk of heparin-induced thrombocytopenia in MPN patients, a careful monitoring of the total platelet count during the heparin treatment is of crucial importance [5]. Finally, antiplatelet therapy also warrants the strict monitoring of total platelet count, especially in MPN patients with the need of cytoreductive therapy, since thrombocytopenia is a frequent finding during COVID-19 and particularly in primary MF, being severe in 23% of patients (under 50×10^9/L) [27].

The risk of thromboembolic complications in patients with MPN and COVID-19 constellation: the need for comprehensive evaluation. The authors [15], while discussing the obtained results, highlight the need for accounting the numerous factors, confounding the risk of arterial thrombosis in MPN patients with COVID-19. In particular, the enrolled cohort of MPN patients was characterized by the higher rates of traditional cardiovascular and thrombotic risk factors, including hypertension, AF, smoking and atherosclerotic disease, in comparison to those without MPN. In addition, one should also consider the impact of vaccines and different antiviral therapies, as well as the changes of cytoreductive, immunosuppressive and antithrombotic therapy while switching from out- to in-patient settings [15]. Therefore, the comprehensive evaluation of various confounding factors, with the consequent development of validated clinical risk scores, may be helpful for optimizing the strategies of antithrombotic prophylaxis in MPN patients affected by COVID-19, including the hospitalized ones [15, 55].

Current principles of antithrombotic prophylaxis in patients with hematological malignancies in the setting of COVID-19: a brief summary. The recently published ESMO-EHA Interdisciplinary Expert Consensus [56] once again stated an increased risk of thromboembolic events and associated complications, such as lung vessel obstructive thrombo-inflammatory syndrome, in patients with hematological malignancies and SARS-CoV-2 infection, including those with MPN. Considering the number of hemostatic alterations associated with COVID-19, the experts emphasize that the antithrombotic prophylaxis in patients with hematological malignancies should be continued according to existing guidelines. Importantly, such patients should be carefully and as routinely as possible monitored with the aim to prevent possible bleeding complications. The hospitalized patients with verified COVID-19 should receive LMWH or fondaparinux as the options for antithrombotic prophylaxis. Of note, the use of UFH is addressed to critically ill patients with a significantly reduced kidney function. When DOAC are used for prevention of thromboembolic events, the potential drug-drug interactions must be thoroughly reviewed. At the same time, the role of full therapeutic anticoagulation in severely ill COVID-19 patients remains controversial [56].

CONCLUSIONS

MPN and pandemic SARS-CoV-2 infection (COVID-19) are both conditions with inherently enhanced susceptibility to thromboembolic complications. Along with the specific pathophysiological pathways, MPN and COVID-19, in case of their constellation, share overlapping pathomechanisms of hypercoagulability. The analysis of currently available references suggests the ongoing accumulation of basic, epidemiological and clinical data regarding various aspects of thrombosis/thromboembolism in MPN patients with concomitant COVID-19. It is likely, that patients with MPN are more prone to be affected by thromboembolic events in the setting of SARS-CoV-2 infection. At the same time, the issue on additive impact of MPN and COVID-19 on the thrombotic risk remains challenging, being a matter of scientific debates and a subject for future research. Considering the relatively low prevalence of

MPN, and the absence of specific «hemostasiological» guidelines, devoted to MPN in tandem with SARS-CoV-2 infection, the conduction of global registry studies is of crucial importance, aiming to provide a continuous and thorough collection and analysis of the data, related to the characteristics of this particular patients' population, pathological background, clinical behavior and outcomes. The comprehensive study of such the data, along with their pathophysiological interpreting, is a multidisciplinary task, which should be performed with an ultimate goal to improve already implemented and develop novel approaches to antithrombotic management of patients with MPN and concomitant COVID-19.

FUTURE PERSPECTIVES

In the context of future research in the field of thrombotic/thromboembolic events in MPN patients in the setting of COVID-19 [2, 5, 15, 57-59], a number of directions deserve attention, in particular the following: better understanding of epidemiology of thrombosis and bleeding; further elucidating the SARS-CoV-2 infection-induced changes in hematological malignancies, including MPN, and coagulation manifestations as prognostic markers in the prediction of disease severity; deepening one's knowledge on the basic and clinical aspects of thrombotic risk cumulating in case of MPN/COVID-19 constellation; shedding the light on the specific role of platelets in the lungs in the development of pulmonary embolism in MPN patients, infected by SARS-CoV-2; the impact of different SARS-CoV-2 variants on the epidemiology of thromboembolic complications, their pathophysiological features, and outcomes in MPN patients; thorough evaluation of numerous clinical, molecular, laboratory and instrumental factors, aiming at the development of appropriate risk scores, with the consequent detection of the most vulnerable groups of patients and improvement of clinical decision-making; handling the tasks regarding the better choice of the regimen of acute and long-term antithrombotic therapy, considering the results of comprehensive confounding factors analysis; the reveal of novel therapeutic approaches to reduce the thrombotic and bleeding risk; the use of anthithrombotic therapy in the context of rapidly growing area of immunology, immunotherapy, malignancy microenvironment and vaccination; further long-term follow-up of patients with MPN and COVID-19, with a special emphasis on systematic reviews and meta-analyses to estimate the risk of death and other important outcomes of these patients, together with thromboembolic and major bleeding complications; conducting larger follow-up studies, expectantly not having the limitations inherent to already carried out exploratory research; integrating the results of basic, translational and clinical studies, including the evidence from national and global registries.

CONFLICTS OF INTEREST

Nothing to declare.

ETHICAL APPROVAL

Not applicable (no animals or human subjects were used in this study).

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Резюме

COVID-19 У ПАЦІЄНТІВ З МІЄЛОПРОЛІФЕРАТИВНИМИ НЕОПЛАЗІЯМИ: РИЗИК ТРОМБОЕМБОЛІЧНИХ ПОДІЙ ТА СУЧАСНІ МОЖЛИВОСТІ АНТИТРОМБОТИЧНОЇ ПРОФІЛАКТИКИ

О. М. Костюкевич[1], Л. К. Беньковська[1], А. М. Кравченко[1], Т. Я. Чурсіна[2], К. О. Міхалєв[1]

[1] Державна наукова установа «Науково-практичний центр профілактичної та клінічної медицини» Державного управління справами, Київ, Україна

[2] Буковинський державний медичний університет, Чернівці, Україна

Мета: здійснити огляд сучасних літературних даних щодо ризику тромбоемболічних подій та можливостей антитромботичної профілактики у пацієнтів з мієлопроліферативними неоплазіями (МПН) і супутньою коронавірусною хворобою 2019 (COVID-19).

Матеріал і методи. Тематичні наукові праці, опубліковані, здебільшого, впродовж останнього десятиліття (включаючи такі, що стосуються інфекції, викликаної SARS-CoV-2 (COVID-19), – за останні три роки), були використані як матеріал для дослідження. Методологія дослідження передбачала застосування бібліосемантичного методу та структурно-логічного аналізу.

Результати та обговорення. МПН та інфекція SARS-CoV-2 (COVID-19) є станами з підвищеною схильністю до виникнення тромбоемболічних подій (венозних та артеріальних). Поряд зі специфічними патофізіологічними особливостями, МПН та COVID-19, у випадку їхньої констеляції, характеризуються наявністю перехресних патомеханізмів гіперкоагуляції. На сьогодні антитромботична профілактика при поєднанні МПН і COVID-19 (первинна та вторинна) здійснюється відповідно до міжнародних рекомендацій та алгоритмів, що охоплюють як загальні принципи застосування антикоагулянтів (пероральних чи парентеральних) та антитромбоцитарних засобів, – так і специфічні аспекти ведення пацієнтів з МПН чи інфекцією SARS-CoV-2. Ці документи постійно оновлюються у міру появи результатів сучасних досліджень. Зважаючи на відносну невелику поширеність МПН, а також відсутність спеціалізованих рекомендацій, присвячених веденню пацієнтів з МПН та супутнім інфікуванням SARS-CoV-2, надзвичайно важливим стає проведення глобальних реєстрових досліджень. Метою таких досліджень є постійне нагромадження та ретельний аналіз даних щодо характеристик цієї специфічної категорії пацієнтів, патофізіологічного підґрунтя і клінічних особливостей перебігу тромбоемболічних ускладнень, а також короткотривалого і віддаленого прогнозу.

Висновок. Комплексне вивчення фундаментальних, епідеміологічних та клінічних аспектів проблеми тромбозів/тромбоемболій при констеляції МПН/COVID-19 – є мультидисциплінарним завданням, вирішення якого сприятиме поліпшенню існуючих та розробці нових підходів до антитромботичної профілактики і терапії у таких пацієнтів.

Ключові слова: інфекція SARS-CoV-2, коронавірусна хвороба 2019 (COVID-19), мієлопроліферативні неоплазії, тромбоз, антитромботична профілактика, антитромботична терапія