Therapeutic Implications of Splanchnic Vein Thrombosis

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Splanchnic vein thrombosis (SVT) includes portal (portal vein thrombosis, PVT), mesenteric (mesenteric vein thrombosis, MVT) and splenic vein thrombosis, and Budd-Chiari syndrome (BCS). SVT is generally classified as secondary to an identified risk factor or primitive, unprovoked, when causative factors cannot be identified. While much rarer than common venous thromboembolism (VTE), SVT is often challenging to clinicians for both the identification of the causal disorder and for its therapeutic management. The therapeutic approach of SVT is a clinical challenge and considers the manifestations and the site of thrombosis, the risk of SVT progression, recurrence and bleeding. The decision regarding when to start, as well as the type and the duration of anticoagulant therapy is often made empirically.

splanchnic vein thrombosis | clonal hematopoiesis | myeloproliferative disorders

1. A Role for Direct Oral Anticoagulants (DOACs)

The use of DOACs, specific inhibitors of factor Xa or factor IIa, for the treatment of SVT remains contentious [1]. This is due to the registration trials for DOACs only including patients with PE or DVT: the studies do not include patients with any type of SVT, despite their advantages over anti-vitamin Kappa anticoagulants (VKAs) being relevant for patients with unusual site VTE [2][3][4]. The 2020 ISTH guidelines suggested the possibility of using DOACs in patients without cirrhosis, with acute symptomatic SVT [5]. Retrospective studies and limited prospective data have demonstrated the safety and effectiveness of DOACs compared to VKAs and low molecular weight heparin (LMWH) in this cohort of patients [1][6][7][8]. In a retrospective trial, Naymagon et al. compared the use of DOAC (Apixaban, Rivaroxaban and Dabigatran) with LMWH and Warfarin for the treatment of portal vein thrombosis in patients without cirrhosis. The rate of thrombosis' resolution was higher in patients treated with DOAC than with LMWH of warfarin, and the rate of major bleeding was reduced with the DOAC compared with warfarin [7]. The same authors also analyzed a cohort of patients with PVT and inflammatory bowel disease and similar results were reported concerning the safety and effectiveness of DOACs [6]. A recent study conducted by Ageno et al. evaluated the use of Rivaroxaban to treat portal, mesenteric and splenic vein thrombosis. The RIVA-SVT 100 study is an international, single group assignment, open-label, prospective cohort study; it excluded patients with cirrhosis but included patients with solid cancer, hematologic malignancies and unprovoked SVT. The study showed that the use of rivaroxaban, compared to heparin and VKAs, is safer in terms of bleeding risk; it is also effective considering the recanalization of splanchnic veins at 3 months [8]. Limited data are available

concerning the efficacy and safety of the use of DOACs for secondary prophylaxis of VTE. The prospective study conducted by Serrao et al. compared the use of DOACs with warfarin in the chronic treatment of SVT. There was no difference in the thrombotic events and bleeding rate between the groups. This study suggested that DOACs could represent an effective and safe alternative to warfarin for secondary prophylaxis in SVT patients at high risk of the recurrence of thrombosis [9].

2. Cytoreductive Therapy in MPN-Associated SVTs

In addition to anticoagulation, cytoreductive therapy with hydroxyurea, peg-interferon alfa or the JAK2 inhibitor, ruxolitinib, is offered to all patients with MPN who develop an SVT to reduce the risk of recurrent thrombosis [10]. However, the efficacy of cytoreductive therapy in reducing SVT recurrence, beyond the use of anticoagulation, is not well established. The management of SVT in patients with isolated JAK2 mutations or morphological MPN diagnosis with normal blood counts is debated. In view of the unclear benefits, the cytoreductive therapy is not administered to all patients [11][12].

3. New Insights in SVT: A Role for Clonal Hematopoiesis?

Recently, the increased incidence of clonal hematopoiesis of indeterminate potential (CHIP) in a cohort of idiopathic-SVT [13]. Clonal hematopoieisis (CH) defines a population of hematopoietic cells with one or more somatic mutations or copy number alterations, able to expand overtime with a positive selection pressure. The term CHIP refers to the presence of somatic mutations in leukemia-associated driver genes with a variant allele frequency of more than 2%, in the absence of any hematological cancer [14]. The detection of somatic mutations was reported as a rare condition in young individuals, with an increase above 70 years of age [15]. In this report, patients with CH were associated with an increased risk of mortality for all causes, including cancer development. Interestingly, CHIP has also been associated with an increased risk of cardiovascular disease and, in particular, atherosclerosis [16]. Notably, the modeling of CH in mice was also associated with an increased development of vascular lesions [16], therefore pointing to a potential role for CH in the development of thrombosis. In this respect, CH was shown to be associated with unprovoked pulmonary embolism, suggesting that CH should be considered as a novel risk factor for thromboembolism [17].

While searching for mutations with a next generation sequencing (NGS) approach with MPN associated genes (ABL1, ASXL1, BRAF, CALR, CBL, CEBPA, CSF3R, DNMT3A, ETV6, EZH2, FLT3, HRAS, IDH1, IDH2, JAK2, KIT, KRAS, MPL, NPM1, NRAS, PTPN11, RUNX1, SETBP1, SF3B1, SRSF2, TET2, TP53, U2AF1, WT1, ZRSR2), almost 50% of patients with idiopathic-SVT display somatic mutations. Interestingly, the researchers identified the most frequently mutated gene in DNMT3A. While waiting to be confirmed on larger cohort of patients, the data point to a potential role of specific mutations in increasing the risk of SVT. DNMT3A mutations, together with the TET2 and ASXL1 genes, have the ability to regulate the effect of DNA methylation and, therefore, to modulate gene expression. Interestingly, mutations in the DNMT3A, TET2 or ASXL1 genes have already been reported to increase the thrombotic risk of patients with polycythemia vera. In particular, the presence of at least one mutation

in the TET2, DNMT3A and ASXL1 gene is associated with the increase in risk of vascular events by six folds [18]. It could be speculated that mutations in DNMT3A could modulate the expression of various genes involved in the inflammation response, therefore favoring the development of thrombosis. Further investigations are mandatory to both confirm the pathogenetic role of CHIP in the development of SVT and to assess the pathogenetic mechanism linked to specific mutations.

It is, however, tempting to assume that these results suggest that CHIP should be assessed in the group of idiopathic SVT, offering new insights in the management of these patients. Similar to the observations, other groups have proposed to screen patients with idiopathic-SVT using NGS techniques, allowing the identification of recurrent mutations, such as JAK2-ex12 mutations [19]. Patients with CHIP-associated SVT should indeed represent a novel entity and should require a tighter control over time, due to the risk of progression into a MPN disorder. These patients should also probably require a prolonged anticoagulation due to the potential risk of thrombotic relapse, as observed in MPN patients.

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