SSC Subcommittee Project/Collaborative Project

NAME OF PROJECT: Global Abdominal/Splanchnic Thrombosis Retrospective Observation in Myeloproliferative Neoplasms- GASTRO MPN

Subcommittee: Hemostasis and Malignancy

Person responsible (Chair / Principal Investigator): Kristen Sanfilippo/Mandy Lauw-Rushad Patell

Description Abstract

Scientific Question: What are the outcomes of splanchnic venous thrombosis (SVT) in patients with myeloproliferative neoplasms (MPN); and how these are modulated by MPN-directed therapies, anticoagulation, and antiplatelet therapy.

Background:

Patients with myeloproliferative neoplasms (MPN) are at high risk of venous thrombosis compared to the general population. Although relatively rare in absolute numbers, splanchnic vein thrombosis (SVT) occurs relatively frequently in the context of MPN but remains an understudied field, with limited data to guide clinicians. It is unclear what the association is between MPN molecular (JAK2V617F) burden and the risk of thrombosis, particularly SVT. It also remains unknown if and how cytoreductive therapies (i.e., hydroxyurea, PEG-interferon-a, anagrelide, ruxolitinib or other JAK2-inhibitors, phlebotomy) affect these thrombotic outcomes, whether patients with MPN-related SVT have different short-term and long-term outcomes with respect to portal hypertension, bleeding and recurrent events than patients with SVT in other clinical contexts, and how much SVT impacts survival in patients with MPN.

A significant gap also exists with regards to the choice and duration of anticoagulation for MPN-SVT. Research on the optimal management of MPN-SVT is difficult due to the small number of patients. Antithrombotic management is also challenging due to the increased risk of bleeding as; 1) patients with (MPN-)SVT are at risk for portal hypertension and subsequent esophageal varices, and 2) MPN- or cytoreduction-induced thrombocytopenia. Current studies suggest initiation of anticoagulation treatment for SVT as soon as possible. However, it is not known whether a specific anticoagulation agent is more effective over the other and what the optimal treatment duration is. In addition, the role of aspirin (in addition to or as replacement for anticoagulation) is unexplored. We aim to create a multicenter, international retrospective cohort of patients with SVT-MPN to explore the following items:

1) the outcomes of MPN-SVT including survival and portal hypertension, recanalization, SVT or other recurrent thombosis, bleeding;
2) the impact of cytoreductive therapy on MPN-SVT outcomes;
3) the current use of anticoagulation and antiplatelet options and impact on MPN-SVT outcomes (recurrence, bleeding, portal hypertension, recanalization);
4) the use and impact of endovascular procedures and liver transplantation on MPN-SVT outcomes;
5) the association between patient and disease characteristics and MPN-SVT outcomes.

Design and methodology (Data expected to collect, sample size and statistical analysis):

Study Design:

This will be a multicenter retrospective cohort study evaluating patients at Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), Dana Farber Cancer Institute (DFCI), Mass General Hospital (MGH), Versiti Blood Center of Wisconsin, Mount Sinai Hospital, Masonic Cancer Center at the University of Minnesota, Washington University in St. Louis, and Erasmus University Medical Center in Rotterdam, The Netherlands. Of note, BIDMC, BWH, DFCI, and MGH all belong to Dana Farber Harvard Cancer Center. This study will be approved by respective institutional local ethics committees at all centers to obtain identified data. Each sites' data will then be de-identified prior to submission to Dr. Mandy Lauw, Erasmus University MC, Rotterdam, Netherlands. Deidentified data use agreements are attached.

A study steering committee will meet monthly to discuss research procedures and project updates. Additional centers can participate and contribute patients to the cohort after local ethics approval and consent to the deidentified data use agreement.

Study population (Inclusion, exclusion, eligibility) (patient population; recruitment of participating institutions/physicians and subjects; minimum number needed; expected number):

Inclusion criteria for the cohort study patients will include age greater than 18 years old, with a diagnosis of MPN and objectively diagnosed SVT. MPN will be defined as PV or ET or prefibrotic-MF or PMF or MPN-unclassifiable (MPN-U) based on the National Comprehensive Cancer Network (NCCN) or World Health Organization (WHO) criteria. We will also collect data of patients with JAK2 Clonal Hematopoiesis of Indeterminate Potential (JAK2 CHIP) as defined by the proposed criteria. The date of MPN diagnosis will be the day bone marrow (BM) sample was obtained (if not performed, it will be the day of mutational testing) and it will be up to 1 year from SVT diagnosis. SVT will be defined as a thrombus in hepatic, portal, splenic and/or mesenteric veins confirmed with appropriate imaging (US, CT, MRI, angiography) or laparoscopy/surgery. The date of SVT diagnosis (the date of confirmatory imaging) will be set as the study's baseline.

Data collection will focus on obtaining demographic information, MPN diagnosis and date, MPN disease characteristics including mutations and SVT date and vein affected. We will also collect information about survival and recanalization as well as SVT recurrence, venous thrombosis other than SVT, arterial thrombosis, portal hypertension, bleeding events as complications of MPN-SVT. Finally, we will collect data about MPN-directed therapies, anticoagulation, antiplatelet therapy, and endovascular procedures following SVT diagnosis.

Data will be collected through manual chart review. At BIDMC, the BIDMC Clinical Informatics core will pull specified variables from patient charts, including MPN and SVT diagnosis, as well as demographic information. The other study centers similarly will pull data from their electronic health record systems. Data will be added to separate RedCap or Castor databases at each site. The same structure to the database will be present at each site, however, to allow combination of the de-identified information.

Outcomes:

The primary outcome will be survival after MPN-SVT.

Secondary outcomes will include recanalization, SVT recurrence, venous thrombosis other than SVT, arterial thrombosis, major bleeding, clinical-relevant non-major bleeding, ascites, hepatic encephalopathy, and esophageal varices.

In addition, we will evaluate those outcomes in relation to 1) MPN phenotype and genetic mutations; 2) MPN-directed therapies; 3) anticoagulation treatment; 4) antiplatelet treatment; 5) endovascular procedures following SVT.

Sample Size/Power Calculation

In a study that looked at 12-month mortality in SVT (not MPN related), mortality was 21.7% (survival 78.3%). (PMID: 26945454). A sample size of 320 patients would give us a power of 90% to detect a 10% change (decrease assuming that survival will be worse in MPN-SVT specifically) with an alpha of 0.05.

Statistical Analysis:

The data from all academic sites will be analyzed separately as well as pooled to account for a larger and more representative patient population across the US and the Netherlands. The analysis will be led by a statistician at the Erasmus University MC, Rotterdam, Netherlands and the statistical plan will be vetted with the steering committee statistical analysis. Our variables will be predominantly categorical; therefore, the chi-square test will be used for initial analysis.

The *JAK2V617F* allele burden will be calculated as the ratio of *JAK2V617F* mutation to the sum of mutated (*JAK2V617F*) and wild type *(JAK2*WT) *JAK2* in unfractionated WBCs from peripheral blood or bone marrow. The mutation and wild type of the gene will be measured with rtPCR or next-generation sequencing (NGS) and quantified using standard curves. Similarly, we will calculate the allele burden for other driver mutations possibly present (i.e., *JAK2 exon 12, CALR, MPL*).

Recruitment of Participating Institutions:

Additional sites will be recruited through the SSC subcommittee and members of the steering committee.

Sites joining include:

North America:

USA: Beth Israel Deaconess Medical Center (BIDMC), Brigham and Women's Hospital (BWH), Dana Farber Cancer Institute (DFCI), Mass General Hospital (MGH), Mount Sinai Hospital, Masonic Cancer Center at the University of Minnesota, Mayo Clinic, Virginia Commonwealth University, Washington University in St. Louis, University of Michigan, Duke University, Versiti Blood Center of Wisconsin.

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Europe:

Erasmus University Medical Center, Rotterdam, The Netherlands
University of Insubria, Varese, Italy

Asia:

King Chulalongkorn Memorial Hospital, Bangkok, Thailand
Singapore General Hospital, Singapore

Expected timeline:

IRB submission (completed at all steering sites)

Finalize study design and synchronize variables and data end points: (completed)

Data transfer agreements: December, 2023

Data extraction, cleaning and validation: Q1 2024

Data analysis and interpretation: Q2-3 2024

Submission abstract to scientific meeting: August 2024

Manuscript preparation-submission Q3-4 2024

Expected outcomes (ie. publications):

Publication type (SSC Communication, Guidance document or original article):

- Publication, Original Article:

  We anticipate at least 4 separate manuscripts/ scientific presentations as a result of this effort in this unique population focusing on: impact of anticoagulation on MPN-SVT outcomes, impact of MPN driver mutation on SVT outcomes, impact of cytoreductive therapy on MPN-SVT outcomes; impact of procedural interventions on MPN-SVT outcomes.

- Incorporation into SSC Communication / Guidance Document:

  These results are projected to help generate clinical guidance for clinicians caring for MPN patients with SVT that could be incorporated into a SSSC Guidance Document. It could also generate data to design optimal prospective studies in the future.

Description of project set/up and management, needed infrastructure and resources (summary):

The concept of this project has been discussed during ISTH SSC meetings and an ISTH SSC small grant was awarded in Q4 2023. The project will be discussed during the monthly steering committee meetings

and ISTH SSC meetings. The project will be presented in person at the ISTH SSC meeting during ISTH Congress 2024.

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