

ADVANCES IN HEMATOLOGY

Current Developments in the Management of Hematologic Disorders

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Myeloproliferative Disorder–associated Massive Splenomegaly

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H&O What is myeloproliferative disorder–associated massive splenomegaly?

RM The myeloproliferative disorders (MPDs) are a group of interrelated *BCR/ABL*-negative chronic leukemias that typically encompass essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis. ET and PV both can progress to a myelofibrosis that acts very much like primary myelofibrosis. Though the cause of these disorders is unknown, a subset of patients with MPDs are known to have been exposed to carcinogens (eg, benzene or ionizing radiation), which may have played a role in the development of the disease. These disorders can all lead to enlargement of the spleen. The most significant enlargement of the spleen occurs in individuals with myelofibrosis, either primary or post-ET or -PV. The spleen can enlarge significantly in these patients. Ordinarily, the spleen is 100–300 g, approximately the size of a fist, and well under the ribcage. With MPD-associated splenomegaly, there have been reports of spleens up to 10 kg, which fill much of the abdomen and extend into the pelvic region. This enlargement of the spleen, it is believed, is due to white blood cells leaking out of the bone marrow and accumulating in the body. This process is known as extramedullary hematopoiesis. Of the organs, the spleen has the greatest affinity for these white blood cells, causing them to accumulate in it. Under the microscope, the tissue of the spleen in this condition appears similar to that of bone marrow, with a great deal of new cells generating. Extramedullary hematopoiesis can occur anywhere in the body, though the spleen is the most common site. Other locations of this accumulation reported include the liver,

and, more rarely, the pericardium, the spinal canal, the lung, and the skin. Enlargement of the spleen is thus a side effect of MPDs.

H&O Why is splenomegaly a problem?

RM First, splenomegaly can cause a variety of mechanical symptoms, ranging from discomfort to dull, chronic pain to, in extreme cases, severe pain. If the enlarged spleen outstrips the blood supply, splenic infarct can occur, wherein small areas of the spleen die, resulting in extreme pain. Additionally, a greatly enlarged spleen can be the size of a full-term pregnancy or larger. Bowel function can be impaired by splenomegaly as the spleen fills the abdominal cavity, causing constipation or irregularity. Early satiety can also occur if the spleen presses on the stomach. Breathing can be impaired to a degree by causing a feeling of shortness of breath.

H&O Is treatment aimed at curing the MPD or its side effect, the enlarged spleen?

RM Because MPDs are difficult to treat, without a clear and effective method of cure, clinicians are faced with treating the side effect—splenomegaly—rather than the underlying disorder. The most aggressive treatment for MPDs is stem cell transplantation, but not many patients are candidates for this therapy. Therefore, most available therapies do not induce remission, which has led to the search for ways to manage the resulting splenomegaly. The three types of therapeutic management are surgical, medicinal, and radiotherapeutic.

H&O When is surgery used to treat splenomegaly?

RM Splenectomy is one potential therapy for this condition. Because MPDs inherently are diseases of the bone marrow, removing the spleen does not improve the

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natural history of the disease. The bone marrow does not improve, or worsen, with the removal of the spleen. Patients with overwhelming symptoms from the enlargement of the spleen are considered for surgery because the risk of surgery is considered worthwhile. Once the spleen has been removed, the symptoms that affect the patient's quality of life resolve. The associated pain, discomfort, and lack of appetite are all improved by surgical therapy. The negative aspect of removing the spleen is the risk of postoperative complications. At Mayo Clinic, a surgical mortality rate of 6–9% has been observed in these patients in the first 30 days following surgery. Complications tend to arise from blood clots or from bleeding either during or after surgery. Patients with MPDs have an increased risk of bleeding from any type of surgical procedure. A recent study showed that overall, with elective surgery in a patient with an MPD, the risk of thrombosis and bleeding is approximately 7%. Furthermore, in approximately 10% of patients who have undergone splenectomy in this setting, the liver subsequently enlarges due to extramedullary hematopoiesis and becomes a problem. Typically, the liver enlarges after splenectomy but not to the same degree as the spleen has enlarged.

There is a common misperception that the spleen is producing new blood cells and, therefore, splenectomy will cause blood counts to decrease. In reality, after splenectomy, an increase is typically observed in red and white blood cell and platelet counts. An unsafe increase in the white blood cell and/or platelet count can occur unexpectedly after surgery, which may require use of hydroxyurea to decrease those counts.

H&O How else is hydroxyurea used in MPD-associated massive splenomegaly?

RM Hydroxyurea can be used in two ways in this setting. As indicated, hydroxyurea is used to decrease the risk of blood clots and bleeding postsurgically in patients with MPDs by controlling the platelet count and potentially the white blood cell count. Second, hydroxyurea can also be used to shrink the size of the spleen. To do so, a relatively large dose (2,000–3,000 mg/day) must be used. However, at this dose, the hydroxyurea may shrink the spleen and cause improvement in symptoms but also decrease the white blood cell and platelet counts to unsafe levels. Therefore, it can be difficult to balance the amount of hydroxyurea needed to shrink the spleen with the amount that can negatively affect blood counts overall. Typically, when an improvement in symptoms is seen with hydroxyurea, the spleen has decreased in size by 20–30%. Although the spleen does not return to normal size, this decrease can be sufficient to improve the patient's symptoms.

H&O What other medicinal treatments are used to treat MPD-associated massive splenomegaly?

RM Successful, aggressive medicinal treatments include the intravenous chemotherapies cladribine (5 mg/m² for 5 consecutive days) and daunorubicin as single agents. A response rate of 30% in patients with splenomegaly has been observed with low doses of thalidomide (Thalomid, Celgene) or lenalidomide (Revlimid, Celgene). Other types of chemotherapies, including melphalan and busulfan, have been tried. These agents, however, can increase the risk of the MPD transforming into acute leukemia, therefore their use is uncommon. These chemotherapeutic treatments fundamentally are used to decrease myeloproliferation and help with symptoms but they do not seem to have a significant impact on the underlying disease course. Therefore, an active clinical trial program is currently seeking better treatments.

H&O When is radiotherapy indicated in this setting?

RM Radiotherapy can help to decrease problems with accumulation of cells in various areas in the body in patients with MPDs. Radiotherapy can help to shrink the spleen and the liver, though the liver is less tolerant of radiation than the spleen. Radiotherapy has also been used when cells have accumulated in the spinal canal or the lungs. Radiation, however, can overly decrease the white blood cell and platelet counts when used to treat splenomegaly. An abscopal effect of suppressing the bone marrow sometimes occurs. In this situation, patients do not experience symptomatic relief or the relief tends to be of limited duration. Radiotherapy can be used repeatedly if symptomatic relief is needed. However, the abscopal effects tend to lead to scarring in the spleen. As a result, if subsequent splenectomy is needed, the surgery becomes more dangerous. Therefore, radiotherapy tends to be used only in those patients who are thought not to be candidates for later surgery. Elderly patients or patients with severe comorbidities who are suffering from the symptoms of splenomegaly are the best candidates for radiotherapy.

H&O What experimental therapies are under investigation in this setting?

RM The most promising experimental therapies in this setting are the JAK2 inhibitors, including INCB018424 (Incyte), XL019 (Exelixis), lestaurtinib (Cephalon), and others. JAK2 is a protein in the JAK/STAT pathway that is involved in cell growth and differentiation. Several types of mutations have been found to be common in individuals with these diseases. Specifically, the JAK2V617F

mutation is believed to be partially—though not completely—responsible for MPDs. Other mutations in MPL pathways are also thought to signal through JAK2. The lead JAK2 inhibitor, INCB018424, was reported at the annual meeting of the American Society of Hematology in 2007 to help to shrink the spleen relatively quickly. Thrombocytopenia was the dose-limiting toxicity. There are ongoing studies attempting to define the dose and the spectrum of activity with JAK2 inhibitors. JAK2 inhibitors appear encouraging as a targeted therapy for individuals with MPD-associated massive splenomegaly, but research is still in its early stages.

There are other agents under investigation. Actimid (Celgene), also known as CC4047, is a thalidomide analog under investigation in an international trial. Both thalidomide and lenalidomide have been found to be helpful in treating MPD-associated splenomegaly. Actimid showed activity preliminarily in this setting. Decitabine (Dacogen, MGI Pharma) is a hypomethylating agent under investigation in this setting due to its activity in

myelodysplastic syndromes and its ability to decrease the levels of accumulating cells.

Suggested Readings

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