

Highlights

- Essential thrombocythemia (ET) is one of a related group of blood cancers known as “myeloproliferative neoplasms” (MPNs) in which cells in the bone marrow that produce the blood cells develop and function abnormally.
- ET begins with one or more acquired changes (mutations) to the DNA of a single blood-forming cell. This results in the overproduction of blood cells, especially platelets, in the bone marrow.
- About half of individuals with ET have a mutation of the *JAK2* (Janus kinase 2) gene. The role that this mutation plays in the development of the disease, and the potential implications for new treatments, are being investigated.
- Individuals with ET may not have symptoms. Patients with signs or symptoms may have burning or throbbing pain in the feet or hands, headaches, dizziness, blood clots or abnormal bleeding episodes.
- ET does not generally shorten life expectancy. Still, medical supervision of individuals with ET is important to prevent or treat complications.

Introduction

Essential thrombocythemia (ET) is one of several “myeloproliferative neoplasms” (MPNs), a group of closely related blood cancers that share several features, notably the “clonal” overproduction of one or more blood cell lines. All clonal disorders begin with one or more changes (mutations) to the DNA in a single cell; the altered cells in the marrow and the blood are the offspring of that one mutant cell. Other MPNs include *polycythemia vera* and *myelofibrosis*.

The effects of ET result from uncontrolled blood cell production, notably of platelets. Because the disease arises from a change to an early blood-forming cell that has the capacity to form red cells, white cells and platelets, any combination of these three cell lines may be affected – and usually each cell line is affected to some degree.

In ET, there is mainly an overproduction of platelet-forming cells, called “megakaryocytes,” in the marrow. This results in the release of too many platelets into the blood. A platelet is a small blood cell. Its function is to start the process of forming a plug (clot) in response to blood vessel injury in order to prevent or minimize bleeding. When platelets are present in very high numbers they may not function normally and may cause a blockage in blood vessels, known as a “thrombus.” Less often, a high number of platelets can also cause bleeding problems.

Another word for platelet is “thrombocyte.” The term “thrombocythemia” means an excess of platelets in the blood. The term “essential” indicates that the increase in platelets is an innate problem of the blood cell production in the bone marrow. “Secondary thrombocytosis” is the term for a condition that results in very high platelet counts in the blood in reaction to another problem in the patient’s body, such as inflammatory disease, removal of the spleen, or iron deficiency in adults. A patient with secondary, or reactive, thrombocytosis should have a return to normal platelet count in the blood once the primary problem is treated successfully.

This fact sheet about ET provides information regarding diagnosis, treatment, new treatments being investigated in clinical trials and support resources.

Causes

The cause of ET is not fully understood. About half of patients with ET have a mutation of the *JAK2* (Janus kinase 2) gene in their blood cells. Whether or not a patient has the mutation does not appear to significantly affect the nature or course of the disease. Research is under way to determine the precise role of the *JAK2* mutation in the biology of the disease and to identify other mutations in ET patients.

The incidence (newly diagnosed cases) of ET for all races and ethnicities is approximately 2.2 per 100,000 population each year. ET occasionally occurs in older children, but is mostly diagnosed in adult men and women. The prevalence (estimated number of people alive on a certain date in a population with a diagnosis of the disease) is approximately 24 cases per 100,000 population, which has been shown in several small studies.

ET does not generally shorten life expectancy. However, medical supervision is important to prevent or treat thrombosis, a serious complication that can affect vital organs such as the brain or the heart. Also, for untreated pregnant patients with ET, there is a risk to the survival of the fetus.

Signs, Symptoms and Complications

Many patients with ET do not have any symptoms. Patients with signs or symptoms may have:

- Burning or throbbing pain in the feet or hands, sometimes worsened by heat or exercise or when the legs are hanging down for long periods. The skin of the extremities may have a patchy reddish color. “Erythromelalgia,” the medical term for this condition, is caused by diminished blood flow to the toes and fingers (microcirculation).
- Headache, dizziness, weakness or numbness on one side of the body, slurred speech and other signs of inadequate flow of blood to the brain called “transient ischemic attacks” (TIAs).
- Abnormal clotting, called “thrombosis,” which usually occurs in an artery but sometimes occurs in a vein.
- Unexpected or exaggerated bleeding. Abnormal bleeding is infrequent and usually occurs only in the presence of a very high platelet count.
- An enlarged spleen (detected by physical examination or ultrasound imaging). This occurs in about 50 percent of patients.
- Constitutional symptoms like fatigue, weakness, itching, sweating and low-grade fevers, which may be present in advanced cases.

Thrombosis is a more common complication of ET than bleeding. This complication can be very serious if the clot blocks blood flow to an organ, such as the brain (causing a stroke) or heart (causing a heart attack). Older patients with underlying vascular disease may be at highest risk for thrombosis, but there is no precise way to gauge risk. Clotting complications can occur in patients with a slightly elevated platelet count; there is no definitive correlation between platelet number in the blood and risk of thrombosis.

Uncontrolled ET can cause pregnancy complications, including:

- Spontaneous abortion (miscarriage)
- Fetal growth retardation
- Premature delivery
- Placental abruption (premature separation of the placenta and uterus).

Occasionally, ET can transform into another MPN. The disease can also transform into acute leukemia or myelodysplastic syndromes or more serious bone marrow cancers, but this is a very uncommon occurrence.

Diagnosis

Essential thrombocythemia may be considered in symptom-free patients when a blood test (done as part of a periodic health examination) shows a higher than normal platelet count. Or, a doctor may order blood tests and note a markedly elevated platelet count for a patient who has a blood clot, unexpected bleeding, or a mildly enlarged spleen.

A platelet count is measured as part of a blood test called a “complete blood count” (CBC). Normal platelet values range from about 175,000 to 350,000 platelets per microliter (μL) of blood in most laboratories. ET is a consideration if the platelet count is above 600,000/ μL of blood and remains high over a period of observation. Most ET patients have more than 600,000 platelets per microliter of blood. Rarely, ET is diagnosed in patients with platelet counts that are high normal (between 350,000 and 600,000 platelets per microliter of blood). Further examination and testing are needed to rule out other conditions that could be the cause of the patient’s high platelet count (reactive or secondary thrombocytosis).

The diagnosis of ET is made on the basis of

- A high platelet count that persists over time
- The presence of the of *JAK2* mutation (found in about half of ET patients) or any other molecular or genetic abnormality in the patient’s blood or bone marrow cell

- The absence of evidence for other clonal blood diseases that can be accompanied by increased platelets (usually requires examination of the bone marrow) and no evidence for any other condition that would cause a reactive increase in platelets.

Although a bone marrow examination is not strictly necessary to make the diagnosis, it is often done because it can help to confirm the diagnosis and to exclude other bone marrow diseases that can cause high platelets. The marrow of a patient with ET shows a significant increase in platelet-forming cells (megakaryocytes) and masses of platelets.

Generally, a doctor will consider other conditions first to determine if any of them are the cause of the increase in platelets. Several conditions can cause an increase in platelets; for example:

- Inflammatory disorders such as active arthritis or gastrointestinal inflammatory disease
- Iron deficiency anemia
- An undetected (occult) cancer
- History of splenectomy (removal of the spleen).

Treatment Planning

Treatment decisions are based on the patient's risk for clotting or bleeding complications. For some patients with no signs of the disease other than an increased platelet count, the risk of complications may be low and no therapy is needed. On the other hand, in patients with previous bleeding or clotting episodes, or in patients who are at high risk for such complications, doctors may use medications to reduce high platelets.

Risks for clotting complications (thrombosis) include:

- A history of a clot
- Advanced age (over 60 years)
- Cardiovascular risk factors, such as high cholesterol, diabetes, smoking, obesity or hypertension— all considered by many doctors as additional risk factors for thrombosis.

Every patient's medical situation is different and should be evaluated individually by a hematologist or oncologist who specializes in treating blood cancers. It is important for you and members of your medical team to discuss all treatment options, including treatments being studied in clinical trials.

For more information about choosing a doctor or a treatment center, see the free LLS publication *Choosing a Blood Cancer Specialist or Treatment Center*.

Treatment

A hematologist (a doctor who specializes in blood disorders) can recommend specific treatment and management for a patient with ET.

Patients with low risk for clotting are usually observed without any therapy; low-dose aspirin can be considered. Patients with high risk for clotting require medical therapy to decrease platelets to normal levels, and are given low-dose aspirin to prevent clotting.

A risk factor for bleeding can include a very elevated platelet count (over 2 million platelets per microliter of blood). Therefore, in a young patient with low risk for clotting but with an extremely high platelet count, one should be aware of the increased risk of bleeding. In this case, use of medications to lower an extremely high platelet count should be considered, but aspirin should be avoided as it may contribute to bleeding risk (at least until the number of platelets has been decreased).

Drug Therapy

The drugs most commonly used to treat ET are hydroxyurea (Hydrea®), anagrelide (Agrylin®) and interferon alfa (immediate-release preparations Intron® A and Roferon-A® and sustained-release preparations PEG-Intron® and Pegasys®).

Hydroxyurea (Hydrea®)—This myelosuppressive drug (an agent that suppresses the marrow's production of blood cells), a chemotherapeutic agent, can be used as initial therapy for ET. Hydroxyurea, given by mouth, is often successful in decreasing the platelet count within several weeks, with few short-term side effects. In some patients it may lower red blood cells, causing anemia; other rare side effects are mouth ulcers, change in the sense of taste, skin ulcers or rash. There is some controversial evidence that hydroxyurea is associated with an increased risk of developing acute leukemia after long-term therapy and is frequently avoided as therapy for younger patients. However, it is thought to have much less potential for causing leukemia than other myelosuppressive agents, such as radiophosphorus, and alkylating agents, such as melphalan (Alkeran®), chlorambucil (Leukeran®) and others.

Low-dose aspirin—Aspirin, given by mouth, is effective for patients at high risk for clotting complications and is commonly prescribed. In patients with low risk for clotting, evidence for its use is less strong. It may also increase bleeding risk in patients with extremely high platelets. For these reasons, the use of aspirin in treating ET needs to be individualized. Pregnant patients may be treated

with low-dose aspirin to reduce the risk of miscarriage, fetal growth retardation, premature delivery or other complications. Aspirin should be avoided for at least one week prior to delivery to reduce any risk of bleeding complications in the mother or the newborn.

Anagrelide (Agrylin®)—This is a non cytotoxic drug (an agent that does not kill cells) that effectively decreases platelet formation in most patients and is given by mouth. It has not been associated with increased risk for leukemia and is a therapy alternative to other treatments, such as hydroxyurea. Side effects of anagrelide can occur, including fluid retention, heart and blood pressure problems, headaches, dizziness, nausea and diarrhea.

Interferon alfa (immediate-release preparations Intron® A [alfa-2b] and Roferon-A® [alfa-2a] and sustained-release preparations PEG-Intron® [peginterferon alfa-2b] and Pegasys® [peginterferon alfa-2a])—Another treatment for lowering platelet counts in patients with ET. However, it is not used in most patients because, in comparison with other treatments for ET, it is less convenient to administer—it is given by intramuscular or subcutaneous injection—and may cause troublesome side effects. Some patients experience moderately severe flu like symptoms, confusion, depression or other complications. Development of sustained-release preparations provides a new option for patients; injections would be weekly, a regimen patients tend to tolerate better (particularly in the case of Pegasys).

Plateletpheresis—This is a process that uses a special machine to skim platelets from a patient's blood and then return the plasma (the liquid portion of blood) and red cells to the patient. It is used only in emergency situations, such as acute clotting complications, when the platelet count is very high and needs to be reduced quickly. The platelet-reducing effect of this therapy is temporary.

For specific drug information, see the free LLS publication *Understanding Drug Therapy and Managing Side Effects* and the FDA drug information website www.fda.gov/drugs/resourcesforyou/consumers/default.htm.

Talking to Your Doctor About Side Effects of Treatment

Side-effects management is important. If you are having any concerns about your side effects, talk to your doctor to get help. Most side effects are temporary and resolve when treatment is completed.

The individual side effects of specific drugs are discussed in the treatment section beginning on page 3.

Treatments Under Investigation

LLS invests research funds in ET and other blood cancers. LLS is funding research related to identifying and effectively attacking targets in ET and other MPNs for new drug therapies, new approaches to classification, diagnosis and therapy. Research is also being funded to investigate the mechanism of action of pegylated interferon. The goal is to develop specific and more effective therapy for patients with MPNs.

Clinical trials are carefully controlled research studies, conducted under rigorous guidelines, to help researchers determine the beneficial effects and possible adverse side effects of new treatments. Studies are also conducted to evaluate new indications for therapies that are already approved for other cancers or types of diseases. Patient participation in clinical trials is important in the development of new and more effective treatments for ET and may provide patients with additional treatment options. Patients interested in participating in clinical trials are encouraged to talk to their doctors about whether a clinical trial would be appropriate for them. For more information about clinical trials, see the free LLS publication *Understanding Clinical Trials for Blood Cancers* or visit www.LLS.org/clinicaltrials.

Some research approaches under investigation include

- Possible genetic origin of MPNs—There is a theory that MPNs may occur in families; if so, they are a group of genetic diseases passed on from one generation to another. This idea is being studied to discover if abnormal genes cause MPNs.
- SAR302503—This Janus kinase inhibitor, given by mouth, is being evaluated to find the efficacy and safety of daily oral doses in patients who are resistant to or intolerant of hydroxyurea.

We encourage you to contact an Information Specialist and visit www.LLS.org for more information about specific treatments under study in clinical trials.

Treatment Outcomes

The median survival for people with ET is near normal. The presence of the *JAK2* gene does not change the median survival. It is important to know that outcome data can show how groups of people with ET responded to treatment, but cannot determine how any one person will respond. For these reasons, patients are advised to discuss survival information with their doctors.

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We're Here to Help

LLS is the world's largest voluntary health organization dedicated to funding blood cancer research, education and patient services. LLS has chapters throughout the country and in Canada. To find the chapter nearest you, enter your ZIP code into "Find your Chapter" at www.LLS.org or contact

The Leukemia & Lymphoma Society

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Callers may speak directly with an Information Specialist Monday through Friday, from 9 a.m. to 6 p.m. ET. You may also contact an Information Specialist between 10 a.m. and 5 p.m. ET by clicking on "Live Chat" at www.LLS.org or by sending an email. Information Specialists can answer general questions about diagnosis and treatment options, offer guidance and support and assist with clinical-trial searches for leukemia, lymphoma, myeloma, myelodysplastic syndromes and myeloproliferative neoplasms. The LLS website has information about how to find a clinical trial, including a link to TrialCheck®, a clinical-trial search service.

LLS also provides free publications that can be ordered via the 800 number or through the "Free Education Materials" option at www.LLS.org/resourcecenter.

Other Resources

MPN Education Foundation

www.mpdinfo.org

The MPN Education Foundation provides information, education and support and looks to advance research and develop drugs to improve the quality of life and care of

patients with myeloproliferative neoplasms (MPNs). The foundation provides patient and doctor conferences and facilitates patient participation and accrual in clinical studies and surveys.

The MPN Research Foundation

www.mpnresearchfoundation.org

The MPN Research Foundation is a nonprofit organization whose primary mission is to promote, fund and support the most innovative and effective research into the causes, treatments and potentially the cure of essential thrombocythemia, polycythemia vera and myelofibrosis. The organization also provides information and support to people who have myeloproliferative neoplasms.

The Myeloproliferative Disorders Research Consortium (MPD-RC)

www.mpd-rc.org

The MPD-RC is an international, multi-institutional nonprofit consortium funded by the National Cancer Institute. It is set up to coordinate, facilitate and perform basic and clinical research on Philadelphia chromosome-negative myeloproliferative neoplasms (Ph-MPNs).

The National Organization for Rare Disorders (NORD)

(800) 999-6673/(203) 744-0100

www.rarediseases.org

NORD is a unique federation of voluntary health organizations dedicated to helping people with rare "orphan" diseases and assisting the organizations that serve them. NORD is committed to the identification, treatment, and cure of rare disorders through programs of education, advocacy, research and service.

The National Cancer Institute (NCI)

(800) 422-6237

www.cancer.gov

The National Cancer Institute, part of the National Institutes of Health, is a national resource center for information and education about all forms of cancer, including essential thrombocythemia (ET). The NCI also provides a clinical-trial search feature, the PDQ® Cancer Clinical Trials Registry, at www.cancer.gov/clinicaltrials, where ET patients can look for clinical trials.

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