Rare Diseases in Hematology

Target Audience: Physicians (General Practice and Specialists)

Aplastic Anemia

Aplastic anemia (AA) is a rare and life-threatening bone marrow failure syndrome. AA occurs in approximately 2 million patients in Europe and North America each year and has a bimodal incidence pattern, peaking in patients aged 15 to 24 years and over 65 years.[1, 2] AA is caused by T lymphocyte-mediated destruction of hematopoietic stem and progenitor cells.[1] The clinical manifestations of AA include peripheral pancytopenia and bone marrow hypoplasia.[3] Transformation to a clonal myeloid malignancy (such as myelodysplastic syndrome or acute myeloid leukemia) can occur in approximately 15% of patients.[3] If left untreated, the disease is associated with very high mortality. However, treatment advances over recent years have substantially improved survival rates.[4]

Diagnosis

Patients who present with pancytopenia and hypocellular bone marrow should be evaluated for AA.[1] Diagnosis of AA requires exclusion of other clinically similar bone marrow failure syndromes, such as hypoplastic myelodysplastic syndrome, hypoplastic leukemias, paroxysmal nocturnal hemoglobinuria, Fanconi anemia and dyskeratosis congenita.[3] Histologic and flow cytometric characterization, including megakaryocyte and CD34+ blast numeration, are required to distinguish between these diseases.[3] Because the duration between diagnosis to treatment is known to affect overall survival, prompt diagnosis is critical.[3]

Treatment

Upon diagnosis of AA, treatment is determined by the age of the patient and severity of the disease.[1] Disease severity is defined by peripheral blood count values.[3]

For children and young adults with severe AA, bone marrow transplant from an HLA-matched sibling donor is recommended.[1] Including a conditioning regimen with cyclophosphamide and antithymocyte globulin (ATG) prior to transplant is associated with a three-year survival rate of 92%.[1] The primary adverse events associated with a bone marrow transplant approach to treat AA include graft rejection and graft vs. host disease (GVHD), which can be prevented with cyclosporine. In addition, long-term side effects of bone marrow transplant include infertility, hypothyroidism, cataracts and secondary solid malignancies.[3]

In contrast with younger patients, bone marrow transplant has not been associated with improved outcome for patients older than 40 years. For these patients, immunosuppression with horse ATG and cyclosporine A (CsA) is recommended.[1] Adverse events associated with these immunosuppressive therapies include relapse, secondary clonal disorders and post-therapy malignancies.[3]

Patients who are diagnosed with non-severe AA do not necessarily require specific treatment beyond supportive care. While non-severe AA is a fairly indolent disease, treatment with immunosuppressive therapies may decrease the risk of progression to severe AA.[3]

Trends

Some patients with AA are refractory to the current treatment approaches. Therapies currently under investigation may offer new options. Examples include the following:

- Eltrombopag, a synthetic thrombopoetin (TPO)-mimetic, functions by binding and activating the TPO receptor present on hematopoietic stem and progenitor cells and megakaryocytes.[3] Eltrombopag received Breakthrough Therapy Designation from the FDA in January 2018 for frontline treatment of patients with severe AA.[5] Eltrombopag has shown efficacy in producing trilineage hematopoiesis in patients who are refractory to the current treatment options.[3]
- Romiplostim is also a TPO-mimetic. This "peptibody" contains a human immunoglobulin IgG1 Fc domain covalently linked at both C-terminals to two peptides that stimulate the thrombopoietin receptor.[6] Treatment with romiplostim has been shown to improve platelet counts.[7] Because platelet recovery failure is a serious complication after allogeneic hematopoietic stem cell transplant, romiplostim may improve outcomes after transplant. Romiplostim is currently being investigated in phase 2 and 3 trials in patients with AA.[8]

Myeloproliferative Neoplasms

The term "myeloproliferative neoplasm" (MPN) encompasses a variety of diseases that result from excessive proliferation of hematopoietic stem cells. These diseases include polycythemia vera, essential thrombocythemia, primary myelofibrosis, chronic myeloid leukemia (CML), chronic neutrophilic leukemia, chronic eosinophilic leukemia not otherwise specified and unclassifiable myeloproliferative neoplasms.[9] MPNs are often chronic conditions that harbor the potential to transform into acute myeloid leukemia. The mutations that drive the aberrant clonal proliferation of hematopoietic stem cells can vary with the different myeloid neoplasms, but mutations in Janus kinase 2 (JAK2) and other cytokine signaling components as well as regulators of chromatin structure and RNA splicing are common.[10]

Diagnosis

MPNs are generally diagnosed by morphological assessment of a peripheral blood smear or bone marrow biopsy.[9,11] Based on the percentage of peripheral blood or bone marrow blasts, the myeloid neoplasm can be classified as an acute myeloid leukemia or chronic myeloid neoplasm. Chronic myeloid neoplasms can be further sub-categorized via morphology assessment and mutation screening. While specific driver mutations alone cannot distinguish one MPN from another, mutations in JAK2, CALR and MPL are known to be associated with polycythemia vera, essential thrombocythemia and primary myelofibrosis, respectively.[9] The presence of a BCR-ABL1 mutation is a diagnostic hallmark for CML.[9]

Treatment

Treatment for MPN depends on the disease subtype. Patients with BCR-ABL1-positive CML are usually treated with tyrosine kinase inhibitors, such as imatinib.[12] For patients with BCR-ABL1-negative MPNs, other approaches are needed.

A common molecular feature of BRC-ABL1-negative MPNs is aberrant regulation of cytokine signaling pathways. Prior to understanding the molecular aberrations in MPN subtypes, treatment options were limited to agents that provided symptom relief.[10] However, the identification of $JAK2^{V617F}$ as the most common driver mutation in BCR-ABL1-negative MPNs led to targeting JAK2 with agents such as ruxolitinib. Ruxolitinib reduced spleen size and disease-associated pathologies, but a considerable number of patients experienced thrombocytopenia and anemia.[10] In addition, only patients with MPNs that activate the JAK/STAT signaling pathway are likely to respond to JAK2 inhibition.

Other efforts to interfere with cytokine-dependent signaling pathways have included targeting phosphatidylinositol 3 kinase (PI3K), mammalian target of rapamycin (mTOR) and AKT. In addition, because mutations in epigenetic regulators are frequently observed in MPNs, these proteins may represent additional points for therapeutic intervention.[10]

Trends

Recent advances in MPN treatment include the investigation of JAK2 and PI3K inhibitors with improved specificity and agents targeting epigenetic regulators.[13] Examples include the following:

- Pacritinib is a JAK2/FLT3 inhibitor that has improved specificity for JAK2 and may have a preferred safety profile. Thrombocytopenia has not been observed with this agent.[14] Pacritinib is currently being investigated in a phase 2 trial in patients with primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis.[15]

- INCB050465 is an inhibitor of the delta isoform of PI3K, which is expressed primarily in hematopoietic cell lineages. This agent is currently being investigated in a phase 2 trial in combination with ruxolitinib in patients with myelofibrosis.[16]
- Guadecitabine, a dinucleotide antimetabolite of decitabine, is a next-generation hypomethylating drug that inhibits DNA methyltransferase. This agent is resistant to cytidine deaminase, which may enable prolonged exposure to decitabine.[17, 18] Gaudecitabine is being evaluated in multiple phase 2 trials for MPN indications.[19]
- ASTX727 is another next-generation hypomethylating agent. ASTX727 combines decitabine with a cytidine deaminase inhibitor (E7727) in a fixed-dose formulation. This combination is intended to improve oral delivery and prevent decitabine degradation in the gut and liver. ASTX727 is being investigated in a phase 3 study in patients with intermediate or high risk myelodysplastic syndromes and chronic myelomonocytic leukemia.[20]

Amyloidosis

Amyloidosis results from systemic or local accumulation of cross-β-sheet amyloid fibrils composed of aggregates of misassembled proteins.[21] More than 30 amyloid proteins have been identified, and amyloidosis can be either hereditary or acquired.[21, 22] Approximately 4,000 patients are affected with the disease each year in the US.[23] Amyloidosis onset is linked to aging and is associated with progressive organ dysfunction that can lead to organ failure and death.[21, 24]

Numerous forms of amyloidosis have been described. The most common form, occurring in 90% of cases, is Ig light chain (AL) amyloidosis. AL amyloidosis arises when clonal or malignant plasma cells produce excessive Ig light chain. AL amyloidosis can affect the liver, heart, kidneys, GI tract and peripheral and autonomous nervous system. The most common hereditary form of amyloidosis is ATTR amyloidosis, which occurs when mutations in transthyretin (TTR), a carrier protein for albumin, cause aberrant TTR accumulation in the nervous system and heart.[25]

Diagnosis

Most patients with amyloidosis present with extreme fatigue, weight loss and edema. Other symptoms vary by patient, depending on the organs most significantly involved. Blood and urine tests (including serum protein electrophoresis with immunofixation electrophoresis (SPEP/IFE), urine protein electrophoresis and IFE or serum free light chain assay) can be performed to diagnose amyloidosis. However, to confirm the diagnosis, amyloid deposition must be detected in a tissue biopsy, usually from abdominal fat pad aspiration, rectal biopsy or bone marrow biopsy.[25]

Treatment

Because amyloidosis is often diagnosed only after significant organ damage has occurred, the initial goal of treatment is to stabilize organ function. Further therapy to treat the underlying cause of the disease is determined by identifying the type of amyloid fibril present. For AL amyloidosis, chemotherapy with alkylating agents such as melphalan or cyclophosphamide is often used to target the underlying plasma cell clone. Immunomodulatory agents (such as lenalidomide or pomalidomide plus dexamethasone) have also been used to treat AL amyloidosis but are poorly tolerated due to fluid retention, fatigue and increases in cardiac biomarkers during therapy.[22] In addition, proteasome inhibitors, such as bortezomib, have shown promise in amyloidosis and are now included in frontline therapy in combination with chemotherapy.

Trends

Several promising agents are under development for the treatment of amyloidosis. Examples include the following:

- Ixazomib is a novel proteasome inhibitor that is more effective at proteasome inhibition and has a more favorable toxicity profile than bortezomib.[22] Ixazomib has shown encouraging efficacy (52% hematologic response rate) in phase 1/2 studies in relapsed or refractory AL amyloidosis.[26] A phase 3 trial in patients with AL amyloidosis is ongoing.[27]
- Daratumumab is a monoclonal antibody against CD38, which is expressed on the surface of clonal plasma cells in AL amyloidosis. Daratumumab has been approved in first-line therapy in patients with multiple myeloma and is currently being evaluated alone and in combination with

chemotherapy and proteasome inhibitors in phase 2 and phase 3 studies in patients with AL amyloidosis.[28, 29, 30]

- Tafamidis meglumine is a small molecule chaperone that binds to and stabilizes wild-type and variant (V122I) TTR. This binding prevents TTR protein misfolding and blocks TTR amyloid fibril formation and deposition. Tafamidis meglumine has shown encouraging results in a phase 3 study in patients with transthyretin cardiomyopathy, for whom there are no alternative approved therapies.[31]

Sickle Cell Disease / β-Thalassemia

β-hemoglobinopathies, including sickle cell disease and β-thalassemia, are diseases caused by defects in the hemoglobin β-globin chain.

Sickle cell disease is caused by a homozygous point mutation in the β-globin gene that leads to aberrant hemoglobin polymerization.[32] This inappropriate polymerization affects the architecture and flexibility of red blood cells, causing them to adhere to the vascular endothelium and obstruct blood flow.[33] Pathological outcomes include inflammation, susceptibility to infection, vaso-occlusion, recurrent pain crises, stroke, organ damage and early death.[34]

β-thalassemia is characterized by loss of expression of the β-globin chain.[34] More than 270 mutations can cause β-globin loss.[35] This absence of β-globin leads to reduced hemoglobin in red blood cells, extreme anemia and ineffective erythropoiesis.[34] In addition, β-thalassemia is associated with deregulation of iron homeostasis, caused by ineffective erythropoiesis and increased intestinal iron absorption. Consequences of iron deregulation include iron deposition into internal organs and parenchymal dysfunction.[35]

Diagnosis

Sickle cell disease can be diagnosed by prenatal or newborn screening to detect the sickle cell gene mutation or sickle hemoglobin protein. Newborn screening is required by every state in the US.[36] However, clinical features may not be obvious at birth and may not appear until adolescence or early adulthood. Vaso-occlusive pain crisis is often the first clinical manifestation of the disease.[35]

Patients with severe cases of β-thalassemia often present in infancy with a failure to thrive, progressive anemia that becomes transfusion-dependent and hepatosplenomegaly.[37] Hemoglobin separation techniques that measure the levels of the different hemoglobin chain variants are used for diagnosis. In addition, DNA-based testing of fetal DNA in maternal circulation can identify β-thalassemia-associated mutations.[37]

Treatment

The only curative treatment available for β-hemoglobinopathies is allogeneic hematopoietic stem cell transplantation. Ideally, patients should receive stem cells from a human leukocyte antigen- (HLA)-matched sibling donor. However, because most patients do not have a matched donor, transplants often require immunosuppressive therapy to reduce the potentially fatal risks of graft rejection, graft vs. host disease and infection.[34]

Trends

In recent years, new agents and approaches have emerged to treat sickle cell disease and β-thalassemia. Examples include the following:

- Voxelotor (previously GBT440) is a small molecule that prevents sickle hemoglobin polymerization and reduces red blood cell sickling.[32] Voxelotor received Breakthrough Therapy Designation in January 2018 for sickle cell disease and is currently being evaluated in phase 2 and phase 3 trials.[38] Earlier clinical studies have indicated that voxelotor increases hemoglobin levels, decreases hemolysis and may increase oxygen delivery to peripheral tissues.[39]

- Rivipansel, a pan-selectin antagonist, is thought to improve blood flow through the microvasculature by blocking cell adhesion and inflammation. Rivipansel is currently being investigated in phase 3 trials for the treatment of patients with sickle cell disease who experience vaso-occlusion pain events that require hospitalization.[40]
- LentiGlobin BB305 is a gene therapy that inserts a functional human β-globin gene into a patient's hematopoietic stem cells prior to autologous stem cell transplantation. LentiGlobin is currently being investigated in phase 1 trials for sickle cell disease and phase 3 trials for β-thalassemia.[42, 43]
- BPX-501 is a T-cell therapy designed to enhance the safety of allogeneic hematopoietic stem cell transplants. BPX-501 consists of genetically modified allogenic donor T cells expressing an inducible human caspase 9 fused to human FK506-binding protein.[44] Treating the patient, who receives BPX-501 cells after autologous stem cell transplant, with the agent rimiducid causes caspase 9 dimerization and activation. The apoptosis that results in these cells can block the development of acute graft vs. host disease.[44] BPX-501B is currently being evaluated in phase 1 and 2 trails for a variety of hematopoietic malignancies and genetic blood disorders, including β-thalassemia.

Hemophilia A/B

Hemophilia A and B are X-linked bleeding disorders caused by the loss of proteins involved in blood clotting. The absence of factor VIII (FVIII) and factor IX (FIX) are causally associated with hemophilia A and B, respectively. These proteins can be lost due to mutation, deletion or gene inversion. Loss of either FVIII or FIX can cause spontaneous bleeds into joints and tissues, which can lead to further susceptibility of the joints to additional bleeding and result in hemophilic arthropathy. In addition, trauma or surgery can cause excessive blood loss in patients with hemophilia.[45]

Diagnosis

Hemophilia A and B are diagnosed by screening and clotting factor tests. These tests may be performed shortly after birth in a newborn if the infant displays unusual bleeding after routine procedures, such as heel stick blood draws or circumcision, or has unusual or frequent bruises. Screening tests include complete blood count (CBC), activated partial thromboplastin time (APTT) test, prothrombin time (PT) test and fibrinogen test. Clotting factor tests to assess the levels of FVIII and FIX in the blood can define the type of hemophilia as well as the disease severity.[46]

Treatment

Treatment for hemophilia involves replacement therapy with clotting factor concentrates. These concentrates of FVIII or FIX, which are either recombinant or derived from plasma, are delivered in instances of acute bleeding or prophylactically to prevent bleeding. However, obstacles with this treatment approach include poor adherence to prophylaxis and the development of neutralizing alloantibodies ("inhibitors") that negate the effect of clotting factor replacements. The emergence of these inhibitors is associated with increased morbidity and mortality. Few treatment options are available for patients whom develop inhibitors; the most efficacious approach is immune tolerance induction, in which the patient receives frequent injections of FVIII or FIX for extended periods of time. However, even with this approach, inhibitors can be eliminated in only 60% and 30% of hemophilia A and B patients, respectively.[47]

Trends

Recent developments in hemophilia treatment include advances in extending the half-life of clotting factor replacement products, agents that minimize inhibitor emergence, gene therapy and RNAi approaches to achieve clotting factor cascade hemostasis.[45] Examples include the following:

- Valoctocogene roxaparvovec is a gene therapy that delivers FVIII to hemophilia A patients. Valoctocogene roxaparvovec received Breakthrough Therapy Designation from the FDA in October 2017 and is currently being investigated in phase 3 trials. Early studies have indicated that this approach can lead to sustained normalization of FVIII activity and stabilization of hemostasis over a period of one year.[48, 49]
- Fitusiran is an RNAi agent targeting antithrombin, causing increased production of thrombin. This elevation of thrombin promotes clotting and prevents bleeding. Fitusiran is being investigated in phase 3 trials as a prophylactic treatment in patients with hemophilia A and B.[50, 51] Early data have suggested that fitusiran causes a significant reduction in the median number of bleeds in patients with hemophilia, including both those with and without inhibitors.[45]

- BAX802 is a recombinant B-domain-deleted porcine FVIII product. Deletion of the B domain results in improved yield in the production of recombinant FVIII.[53] Results from phase 1/2 trials of BAX802 have indicated promising safety and pharmacokinetic outcomes. BAX802 is being investigated in a phase 3 trial in patients with congenital hemophilia A with FVIII inhibitors.[52]
- BAY81-8973 (octocog alfa) is a plasma-free, unmodified, full-length, recombinant FVIII concentrate that does not use products of human or animal origin. BAY81-8973 was approved by the FDA in 2016 for the treatment of children or adults with hemophilia A.[54] BAY81-8973 is currently being evaluated in a phase 3 trial for prophylaxis and breakthrough bleeds in pediatric patients with severe hemophilia A.[55]

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