

# Anemias of Bone Marrow Failure

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**T**he anemias of chronic bone marrow failure are disorders other than iron deficiency, folate deficiency, and vitamin B<sub>12</sub> deficiency in which anemia is present and the reticulocyte count does not increase appropriately. These anemias are commonly (but not always) normochromic and normocytic. The differential diagnosis of the anemias of bone marrow failure is presented in **Table 1**. Although chronic anemia of bone marrow failure generally occurs as a primary problem, it can occur as a secondary problem when a large volume of marrow is treated with radiation therapy.

A peripheral blood smear may suggest which of the anemias of bone marrow failure is present; however, a bone marrow aspirate and biopsy with a cytogenetic analysis is usually necessary for diagnosis. An exception to this is in patients with the anemia of chronic disease, also known as the anemia of chronic inflammation. In patients with a normochromic, normocytic anemia in whom a causative factor is present (eg, renal failure, liver disease, malignancy, rheumatic disease, or chronic infection), a bone marrow examination need not be performed.

This review addresses the diagnosis and management of patients with aplastic anemia, pure red cell aplasia (PRCA), myelodysplastic syndromes, and agnogenic myeloid metaplasia. The anemia of chronic disease and myelophthisic anemia are outside the scope of this review.

## APLASTIC ANEMIA

### Definition

Aplastic anemia is a condition characterized by pancytopenia and hypocellular bone marrow with decreased production of erythrocytes, leukocytes, and platelets. Aplastic anemia may have a devastating clinical course, but it is quite rare. The estimated incidence in developed countries is approximately 2 cases per million, and the incidence appears to be higher in developing countries.<sup>1</sup> This may reflect an infectious etiology; however, a specific agent has not been identified.<sup>2</sup>

### Etiology

Although most cases of aplastic anemia are idiopathic, the condition may occur in patients exposed to high doses of radiation, chemotherapeutic agents, or benzene. Gold compounds and drugs, such as chloramphenicol, methylphenylethylhydantoin (Mesantoin), trimethadione (Tridione), and phenylbutazone, also have a well-documented association with aplastic anemia. Infections such as hepatitis, Epstein-Barr virus infection, HIV infection, and dengue virus have rarely been associated with aplastic anemia. The hepatitis associated with aplastic anemia generally is seronegative, suggesting an infectious agent other than hepatitis A, B, C, D, or E viruses.

Aplastic anemia also has been associated with the syndromes of diffuse fasciitis and eosinophilia, sclerosis of the thyroid gland, Simmonds' disease, and anorexia nervosa.<sup>3</sup> Fanconi's syndrome of pancytopenia, skeletal abnormalities, neurologic disorders, endocrine disorders, chromosomal defects, and increased risk of leukemia is associated with an increased risk of aplastic anemia; this form of constitutional aplastic anemia may present in adulthood without the usual physical signs and may be diagnosed by demonstrating increased fragility of chromosomes.<sup>4</sup> The Schwachman-Diamond syndrome of pancreatic insufficiency and pancytopenia may progress to aplastic anemia or hematologic malignancy.

### Pathogenesis

The pathogenesis of aplastic anemia is heterogeneous. It was originally thought that aplastic anemia represented a failure of stem cells, a failure of the bone marrow microenvironment, or both. However, no defect in cytokine production has been identified, and the bone marrow stroma is of host origin even after

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**Table 1.** Anemias of Bone Marrow Failure

Aplastic anemia
Pure red cell aplasia
Myelodysplastic syndromes
Myelofibrosis
Myelophthitic anemia (including leukemia and marrow replacement by tumor)
Anemia of chronic disease

bone marrow transplantation; therefore, it is unlikely that a problem with marrow stroma is involved. Furthermore, clinical observations have suggested that most cases of aplastic anemia involve an autoimmune mechanism. This mechanism was first suggested after observation of transplant patients who received preparative therapy (including antithymocyte globulin [ATG]) but in whom the transplant failed to engraft. The blood counts in some of these patients improved with cells of host rather than donor origin.<sup>5</sup> Clinical trials using immunosuppressive therapy have supported the autoimmune model of aplastic anemia.<sup>6</sup>

### Symptoms and Clinical Features

The symptoms of aplastic anemia are secondary to anemia, neutropenia, and thrombocytopenia and usually appear insidiously. Patients may present with pallor, petechiae, ecchymoses, epistaxis, gross bleeding, and/or signs of infection. In contrast to other causes of pancytopenia, lymphadenopathy and splenomegaly are not associated with aplastic anemia; if present, these manifestations suggest another cause of pancytopenia (eg, acute leukemia).

At presentation, the hemoglobin concentration in aplastic anemia is often as low as 7 g/dL, with a hematocrit of less than 20%. The reticulocyte count is low, and erythrocyte morphology generally is normal, although some cases may be associated with macrocytosis. The total lymphocyte count usually is normal; therefore, the leukopenia generally is a neutropenia. Although aplastic anemia is a pancytopenia rather than an anemia, patients may present with severe thrombocytopenia or neutropenia prior to developing severe anemia. However, the significance of this characteristic is unknown and may only reflect the fact that erythrocytes have a longer half-life than platelets or granulocytes.

### Diagnosis

The bone marrow examination is helpful not only for ruling in aplastic anemia but also for ruling out other disorders that may present as pancytopenia and mimic

aplastic anemia. Myelodysplasia may present with pancytopenia, but the bone marrow is generally hypercellular with ineffective erythropoiesis. However, myelodysplasia may be hypocellular in 10% to 20% of cases, and in those situations, the distinction between aplastic anemia and hypocellular myelodysplasia may be arbitrary. Often, the presence of an abnormal chromosome is used as a basis for diagnosing hypocellular myelodysplasia, but it is not clear if that practice has clinical meaning. Bone marrow replacement as a result of leukemia may also present as pancytopenia, and distinguishing this disorder from aplastic anemia is relatively easy. Advanced myelofibrosis may be associated with pancytopenia, but the presence of teardrops and nucleated erythrocytes on the peripheral smear and the presence of splenomegaly should give hints as to the diagnosis of myelofibrosis even before a bone marrow biopsy is performed.

As with any disease, there are different degrees of severity of aplastic anemia. Severe aplastic anemia, which is associated with a worse prognosis, is defined as aplastic anemia with moderate or severe marrow hypocellularity any 2 of the 3 following characteristics: neutrophils less than  $0.5 \times 10^3/\text{mm}^3$ , platelets less than  $20 \times 10^3/\text{mm}^3$ , and reticulocytes less than 1% corrected for anemia (ie, percentage of reticulocytes  $\times$  actual hematocrit/normal hematocrit).<sup>7</sup>

### Management

Bone marrow transplantation<sup>8</sup> and immunosuppressive therapy<sup>9</sup> are the primary therapeutic modalities for patients with aplastic anemia. Bone marrow transplantation is the treatment of choice for patients younger than age 30 years who have severe aplastic anemia and a 6/6 human leukocyte antigen (HLA)-matched related donor. For other patients, immunosuppressive therapy is the initial treatment of choice, with bone marrow transplantation reserved for patients who do not respond to immunosuppressive therapy. Transplantation from a matched unrelated donor is a clinical option in young patients who fail immunosuppressive therapy.

**Immunosuppressive treatment.** Several immunosuppressive drugs have been used to treat patients with aplastic anemia, including ATG, cyclosporine, and prednisone, either singly or, more commonly, in combination. Favorable responses have been seen in up to 80% of patients treated with immunosuppressive therapy.<sup>10</sup> Although relapses may occur, 5-year survival rates as high as 87% have been reported.<sup>11</sup>

Many patients experience partial responses to immunosuppressive therapy (ie, blood counts improve but do not normalize). Many of these patients require

chronic administration of cyclosporine to maintain therapeutic response. However, the completeness of remission may not be clinically important in patients who become independent of erythrocyte and platelet transfusions and in whom granulocyte counts are adequate to prevent infection (ie,  $1 \times 10^6$  cells/L). Late development of clonal disorders is more of a concern than a partial therapeutic response. As many as 16% of patients with aplastic anemia who are treated with immunosuppressive therapy develop disorders such as myelodysplasia, acute leukemia, and paroxysmal nocturnal hemoglobinuria.<sup>2</sup> It is not known whether these disorders represent the natural history of aplastic anemia, are caused by immunosuppressive therapy, or represent cases that were incorrectly diagnosed as aplastic anemia. One unifying hypothesis is that the abnormal clone represents an escape from autoimmune attack in aplastic anemia.

Because ATG is a foreign protein, severe or fatal allergic reactions may occur in patients treated with the agent.<sup>11</sup> Skin testing prior to use of ATG is essential, and an anaphylaxis kit should be present during all drug administrations. To prevent allergic reactions, patients can be desensitized to ATG. Alternatively, anti-lymphocyte globulin (ALG), which is produced in rabbits, may be used instead of horse-derived ATG. The administration of foreign proteins also may result in serum sickness 1 to 2 weeks following therapy. The risk of serum sickness can be markedly decreased by administering prednisone in conjunction with ATG and using a prolonged corticosteroid taper.

An alternative immunosuppressive approach is to administer large doses of cyclophosphamide—similar to those used in transplantation but not accompanied by administration of stem cells.<sup>12</sup> Although initial results were encouraging,<sup>12</sup> a randomized trial comparing cyclophosphamide to ATG was terminated prematurely due to excess toxicity in patients treated with cyclophosphamide.

**Bone marrow transplantation.** For patients treated with bone marrow transplantation, long-term survival rates as high as 90% have been reported at single institutions,<sup>8</sup> with survival rates of 75% reported in registry data. Because the major cause of death in bone marrow transplant patients is graft-versus-host disease, and because the incidence of this complication increases with age, results are better in children than in adults. Unfortunately, attempts to decrease the incidence of graft-versus-host disease by means of T-cell depletion have led to an increase in graft failure.

The best results using allogeneic transplantation have been reported when matched related donors are

used. Matched unrelated donors also have been used to treat aplastic anemia, but results generally have been less favorable than those achieved with related donors. However, until recently, unrelated donors were matched primarily by serologic techniques rather than by DNA technology. Therefore, as techniques for matching become more sophisticated, results of transplantation using unrelated donors may improve and approach those achieved when related donors are used.

## PURE RED CELL APLASIA

### Clinical Presentation and Etiology

PRCA is associated with severe anemia but normal levels of granulocytes and platelets are present. Reticulocyte counts are markedly decreased to less than 1% in all cases and to less than 0.1% in some cases. Analysis of bone marrow shows absence of erythrocyte precursors despite the presence of normal megakaryocytes and normal stages of granulocyte maturation.<sup>13</sup>

Most PRCA cases are of immunologic origin, with antibodies directed against various stages of erythrocyte precursors. Other immune mechanisms may be present, as PRCA rarely has been associated with antibodies to erythropoietin and with T-cell destruction of erythrocyte precursors.<sup>14,15</sup> PRCA may also occur as a complication of human parvovirus infection.<sup>16</sup> Additionally, there is a congenital form of PRCA, the Diamond-Blackfan syndrome.

Immune PRCA has been associated with conditions that reflect an altered immune system, including thymoma, prior administration of azathioprine, rheumatoid arthritis, systemic lupus erythematosus, hepatitis, infectious mononucleosis, lymphoma, chronic lymphocytic leukemia, and large granular lymphocyte syndrome.<sup>17–20</sup> PRCA has also been associated with Hodgkin's disease, non-Hodgkin's lymphoma, myeloma, acute lymphoblastic leukemia, and a variety of solid tumors. Patients with PRCA should always be evaluated for thymoma, which is present in approximately 10% of cases.<sup>21</sup> Removal of the thymoma may lead to remission in some cases of PRCA.<sup>21</sup> Patients with PRCA should also be evaluated for the presence of parvovirus B19.

In most individuals, exposure to parvovirus B19 results in transient infection. In these individuals, anemia does not develop before the immune system clears the virus because the lifespan of erythrocytes is longer than the period of viral infection. In patients with hemolytic anemia (eg, sickle cell disease or hereditary spherocytosis), however, parvovirus B19 infection can cause an aplastic crisis (which is indistinguishable from PRCA) because the erythrocyte lifespan is markedly

**Table 2.** Classification of Myelodysplastic Syndromes

Subtype	Blasts in Peripheral Blood (%)	Blasts in Bone Marrow (%)
Refractory anemia	< 1	< 5
Refractory anemia with ringed sideroblasts*	< 1	< 5
Refractory anemia with excess blasts	< 5	5–20
Refractory anemia with excess blasts in transformation	> 5	20–30
Chronic myelomonocytic leukemia†	< 5	< 20

\*Ringed sideroblasts are at least 15% of nucleated cells in the bone marrow.

†Peripheral blood monocytes  $> 1 \times 10^9/L$ .

shortened and an elevated reticulocyte count is needed to maintain a stable hematocrit. In patients with defects of the immune system (eg, HIV infection), parvovirus B19 infection may persist and thereby cause PRCA. Because PRCA is associated with immune defects, antibody tests for parvovirus B19 may be inadequate to establish a diagnosis and molecular genetics tests for viral DNA may be needed.

### Management

Unless evidence of human parvovirus infection is found, patients are generally treated with immunosuppressive therapy. A brief trial of prednisone usually is the first step, after transfusion of erythrocytes (if required). Fewer than 50% of patients respond to prednisone, however, and cyclophosphamide or cyclosporine is added to the regimen in these patients. Further immune therapy is empirical, including agents such as ATG or intravenous gammaglobulin, until an effective agent is identified.<sup>22,23</sup> After complete remission is achieved, the majority of patients remain in remission for longer than 5 years. Anemia is the only clinical problem in patients with PRCA and can be remedied by transfusion of erythrocytes; therefore, mortality of PRCA is very low.

Treatment of parvovirus-induced PRCA is intravenous immunoglobulin at doses used for idiopathic thrombocytopenic purpura (ie, 1 g/kg per day for 2 days or 0.4 mg/kg per day for 5 days). Unlike other cases of PRCA, which may require multiple therapies, parvovirus-associated PRCA may respond completely to intravenous immunoglobulin.

## MYELODYSPLASTIC SYNDROMES

### Histologic Features and Subtypes

The myelodysplastic syndromes (MDS) are clonal disorders of hematopoiesis in which bone marrow examination reveals disordered production of erythrocytes, platelets, and granulocytes. The bone marrow is generally hypercellular due to erythroid hyperplasia with ineffective erythropoiesis. Contrary to the name of the disorder, dysplasia may be minimal. Occasionally, megaloblastic features may be present in erythrocyte precursors. Megakaryocytes may have decreased numbers of lobes. Granulocyte precursors generally are normal but may have decreased numbers of lobes. Making a morphologic distinction between MDS and the anemia of chronic disease may be difficult and may depend on the presence of a cytogenetic abnormality that is present in approximately 50% of cases of MDS and is not seen in the anemia of chronic disease. Approximately 75% of patients with MDS are older than 60 years.

MDS traditionally has been subdivided into 5 disorders: refractory anemia (RA), refractory anemia with ringed sideroblasts (RARS), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMML).<sup>24</sup> General features of these disorders as defined by the French-American-British classification system are presented in **Table 2**. The incidence of the subtypes of MDS varies; however, in a recent review of over 800 cases, 36% were found to be RA, 26% were RAEB, 15% were RARS, 15% were CMML, and 8% were RAEB-T.<sup>25</sup>

RA and RARS are relatively benign. Median survival is longer than 5 years, and by 5 years only 10% of patients progress to acute leukemia. The leukemia that occurs in RA and RARS, as in all forms of MDS, is almost always acute nonlymphocytic leukemia. RAEB and RAEB-T are relatively aggressive forms of MDS in which median survival is less than 1 year; more than half of patients with RAEB and RAEB-T develop acute nonlymphocytic leukemia.

RAEB-T is defined by the presence of 20% to 30% blasts in the bone marrow; patients with more than 30% blasts are classified as having acute leukemia (Table 2). This distinction is somewhat arbitrary, and the World Health Organization has proposed setting the dividing line between MDS and acute leukemia at 20%.<sup>26</sup> This stratification is still arbitrary, and distinguishing advanced forms of MDS from acute leukemia is often very difficult. In CMML, only 2 forms of the disease appear to exist. Patients with only moderately elevated monocyte counts ( $< 12 \times 10^6/mm^3$ ) tend to behave in a relatively benign fashion, as if they have RA

**Table 3.** International Prognostic Scoring System for Myelodysplastic Syndromes\*

Prognostic Variable	Score Value				
	0	0.5	1.0	1.5	2.0
Bone marrow blasts (%)	< 5	5–10	—	11–20	21–30
Karyotype†	Good	Intermediate	Poor		
Cytopenias	0 or 1	2 or 3			

\*The risk scores for each prognostic variable are combined to stratify patients into 4 risk groups as follows: 0 = low; 0.5 to 1.0 = intermediate-1; 1.5 to 2.0 = intermediate-2;  $\geq 2.5$  = high.

†Good = normal, –Y, del(5q), del(20q); poor = complex ( $\geq 3$  abnormalities) or chromosome 7 anomalies; intermediate = other abnormalities.

Adapted from Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1998;89:2085. Copyright American Society of Hematology, used with permission.

with elevated monocytes. By contrast, in patients with markedly elevated monocyte counts ( $> 12 \times 10^6/\text{mm}^3$ ), the disease progresses like an aggressive myeloproliferative disorder, carrying a median survival of approximately 1 year.

### Prognostic Classification of MDS

The major limitation of the French-American-British prognostic system is that it considers only the percentage of blasts in blood and marrow. Chromosomal abnormalities are identified in approximately 50% of patients with MDS, with an increased incidence of abnormal chromosomes in those with RAEB and RAEB-T. Chromosome 7 abnormalities and the presence of multiple chromosome abnormalities are associated with an unfavorable prognosis, whereas 5q and 20q abnormalities have a relatively favorable prognosis. The presence of cytopenias in addition to anemia also provides important information about the biology of MDS. These factors have resulted in development of the International Prognostic Scoring System (IPSS) for MDS (Table 3).<sup>25</sup> Median survival according to IPSS score is shown in Table 4. IPSS score can also be used to predict the risk of progression to acute leukemia (Table 5).

### Management

Therapy for patients with MDS often is limited to transfusion support as needed. Erythropoietin alone or in combination with granulocyte colony-stimulating factor (G-CSF) or granulocyte-macrophage colony-stimulating factor (GM-CSF) may decrease the need for transfusions.<sup>27,28</sup> Unfortunately, the patients who respond favorably to growth factor therapy are those who have a minimal transfusion requirement (ie,  $< 2$  U of packed cells/month).<sup>29</sup> Additionally, the high cost of growth factor therapy relative to the cost of transfusion

makes growth factor therapy very cost-ineffective. Furthermore, although G-CSF and GM-CSF can increase the level of circulating neutrophils in up to 90% of patients with MDS and neutropenia, results of a randomized, placebo-controlled trial in patients with MDS showed G-CSF to be associated with a shorter survival time.<sup>30</sup>

Cytopenias in MDS also have been improved with the use of amifostine,<sup>31</sup> 5-aza-2'-deoxycytidine,<sup>32</sup> thalidomide,<sup>33</sup> and arsenic trioxide.<sup>34</sup> However, the long-term impact of these drugs is not clear. As a result, a common approach to treatment of MDS is to treat those with aggressive forms of MDS (ie, RAEB or RAEB-T) with antileukemic therapy. Although remissions are achieved in the majority of cases, such remissions are often very brief.

An alternative approach is to employ allogeneic stem cell transplantation,<sup>35</sup> which is the only curative treatment for patients with MDS. Cure rates have been reported in approximately 40% of patients treated with this modality. The best results are achieved in younger patients with the most favorable subtypes of MDS; however, these patients also have the best results in the absence of transplantation. Standard criteria for selecting patients with MDS for transplantation do not exist, but Anderson<sup>35</sup> has recommended that allogeneic bone marrow transplantation should be performed in patients with high- or intermediate-risk disease and should be considered for younger patients (age  $< 40$  years) with low-risk disease and a single life-threatening cytopenias.<sup>35</sup>

Recently, reduced intensity allogeneic transplants (nonmyeloablative transplants) have been used in MDS.<sup>36</sup> This approach relies less on high-dose therapy, and more on the graft versus leukemia phenomenon to eliminate the abnormal clone. Although this approach is associated with less early mortality compared with

**Table 4.** Median Survival in Myelodysplastic Syndromes by IPSS Risk Group

IPSS Risk Group	Median Survival (y)	
	Patient Age ≤ 60 y	Patient Age > 60 y
Low	11.8	4.8
Intermediate-1	5.2	2.7
Intermediate-2	1.8	1.1
High	0.3	0.5

IPSS = International Prognostic Scoring System.

Data from Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1998;89:2086.

routine allogeneic transplantation, results using this approach are preliminary.

### AGNOGENIC MYELOID METAPLASIA Pathophysiology

Agnogenic myeloid metaplasia (AMM), also known as myelofibrosis, is a clonal stem cell disorder characterized by extramedullary hematopoiesis and bone marrow fibrosis. The bone marrow fibrosis in AMM is polyclonal and is likely reactive to the clonal hematopoietic disorder.<sup>37,38</sup> A clinically identical disorder, secondary myelofibrosis, may occur in patients with polycythemia vera. Although the etiology of marrow fibrosis in AMM is unknown, a favored hypothesis is that the fibroblast proliferation may be related to platelet-derived growth factor.<sup>39</sup>

Extramedullary hematopoiesis in AMM recapitulates the sites of hematopoiesis in the fetus. Production of cells can take place in any organ, but splenic production is most common, followed by production in the liver. Rarely, extramedullary production of cells near the spinal cord has been associated with neurologic symptoms.<sup>40</sup>

### Clinical Features

The median age at diagnosis of AMM is 60 years. Patients may be asymptomatic at diagnosis or may present with symptoms related to anemia, thrombocytopenia, or splenomegaly (ie, abdominal fullness, early satiety, or left upper quadrant pain). Patients also may report fatigue, weight loss, low-grade fever, and night sweats.

Splenomegaly is the most common abnormal finding on physical examination. On the average, the spleen grows 1 cm below the costal margin per year, but the growth rate varies greatly. Therefore, over sev-

**Table 5.** Progression to Leukemia in Myelodysplastic Syndromes by IPSS Risk Group

IPSS Risk Group	Time to Development of Acute Leukemia (y)*	
	Patient Age ≤ 60 y	Patient Age > 60 y
Low	> 9.4	9.4
Intermediate-1	6.9	2.7
Intermediate-2	0.7	1.3
High	0.2	0.2

IPSS = International Prognostic Scoring System.

\*Time at which 25% of patients had developed acute leukemia.

Data from Greenberg P, Cox C, LeBeau MM, et al. International scoring system for evaluating prognosis in myelodysplastic syndromes. *Blood* 1998;89:2086.

eral years patients can develop splenomegaly that fills the left side of the abdomen.<sup>41</sup> Portal hypertension is uncommon but may lead to ascites, varices, and gastrointestinal bleeding.

Blood counts are highly variable in patients with AMM. Anemia is common and reflects decreased production and hypersplenism. A peripheral blood smear is generally very informative, with teardrop forms and nucleated erythrocytes seen in nearly all cases. Leukocyte counts are increased in approximately 50% of cases and decreased in 25% of cases at diagnosis.<sup>41</sup> Myelocytes and metamyelocytes are commonly seen in the peripheral blood. Blast cells are occasionally seen but do not indicate a leukemic transformation unless the percentage of blasts approaches 20%.<sup>42</sup> Platelet counts may be normal, increased, or decreased at presentation and generally decrease in association with hypersplenism as the disease progresses.

A peripheral blood smear may strongly suggest the diagnosis of AMM, but diagnosis is established by analysis of a bone marrow biopsy specimen that reveals marked fibrosis. Early in the course of disease, the bone marrow may be cellular (the so-called *cellular phase* of AMM), but some degree of increased fibrosis and osteosclerosis is likely to be present.<sup>43</sup> As in MDS, megakaryocytes may be abnormal and micromegakaryocytes may be seen. Abnormal lobulation may be observed, although granulocyte precursors may be normal.

The majority of patients with AMM survive between 3 and 7 years from diagnosis, but approximately 20% survive for more than 10 years.<sup>41</sup> Recently, a prognostic model for AMM has been presented which bases prognosis on 2 variables, the presence of anemia

(hemoglobin < 10 gm/dL) and the presence of an abnormal leukocyte count (lower than  $4.0 \times 10^3/\text{mm}^3$  or greater than  $30.0 \times 10^3/\text{mm}^3$ ).<sup>44</sup> The major causes of death in AMM include infection and hemorrhage, although thrombosis may occur in patients with markedly elevated platelet counts. Cytopenias generally worsen slowly as splenomegaly increases, and conversion to frank leukemia is uncommon.

### Management

Treatment of AMM generally is supportive. Asymptomatic patients require no therapy except administration of allopurinol if hyperuricemia is present. Anemia can be treated with transfusion support. Androgens, which have been shown to act by augmenting the effect of endogenous erythropoietin, have been used with some success in treating AMM. However, it may be safer to use erythropoietin to avoid the risks of fluid retention associated with androgens.

Chemotherapy has been used to treat patients with AMM. However, patients with massive splenomegaly and marrow fibrosis are very unlikely to tolerate aggressive chemotherapy, and treatment of cytopenias is unlikely to be successful. Radiation therapy has been effective in the treatment of splenomegaly and splenic pain, but the response generally is transient, and the procedure does not eliminate splenic destruction of cells or improve cytopenias.

Splenectomy should be considered in any patient with AMM and recurrent splenic infarcts, early satiety due to massive splenomegaly, or severe cytopenias.<sup>45</sup> The spleen is the major site of hematopoiesis, but production also occurs in the marrow; because splenic destruction of cells is eliminated by splenectomy, worsening of cytopenias is more a theoretical problem than a common clinical occurrence. In some cases, marked elevation of leukocytes or platelet counts may occur following splenectomy. Additionally, production of erythrocytes at extramedullary sites other than the spleen may dominate the clinical picture after splenectomy, as demonstrated by the presence of hepatomegaly and lymphadenopathy.

Because AMM is a clonal myeloproliferative disorder, somewhat similar to chronic myelogenous leukemia, it is not surprising that allogeneic transplantation has been considered in younger patients with AMM. Allogeneic transplantation has been associated with reversal of myelofibrosis in some patients,<sup>46</sup> but the procedure cannot be considered as a standard of care at this time. **HP**

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