REVIEW ARTICLE

Myelofibrosis With Myeloid Metaplasia: Diagnostic Definition and Prognostic Classification for Clinical Studies and Treatment Guidelines

By Giovanni Barosi

Purpose: **Myelofibrosis with myeloid metaplasia (MMM) is a chronic myeloproliferative disorder characterized by bone marrow fibrosis and extramedullary hematopoiesis. Recent studies provide definite diagnostic criteria and prognostic classifications of the disease, and allogeneic stem-cell transplantation (SCT) now offers a chance of curing the disease. In order to put diagnostic criteria and prognostic classifications of the disease into the perspective of developing guidelines for treatment strategies, all studies published in the English literature over the last 30 years were reviewed.**

Materials and Methods: **Studies were identified through a MEDLINE search (1966 to present) and from the bibliographies of relevant articles.**

Results: **The Italian Consensus Conference on diagnostic criteria is a structured enterprise aimed at formulating a definition of MMM that will be used for enrolling patients onto clinical studies. It relies on the obligatory presence of myelofibrosis and on the exclusion of the BCR-ABL rearrangement or Philadelphia chromosome, in association with combinations of traditional features. Prognostic scores allow us to identify classes of patients on the basis of hemoglobin, age, WBC count, and chromosomal abnormalities. Several nonrandomized studies have indicated that allogeneic SCT for patients under the age of 55 is effective in prolonging survival in more than 50% of cases and in possibly curing the disease. Patients with the most severe prognosis are candidates.**

Conclusion: **''Consensus'' methodology offers a definition of MMM useful for conducting and reporting clinical studies. A detailed knowledge of prognostic factors can help to delineate guidelines for addressing patients with allogeneic SCT.**

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MYELOFIBROSIS WITH myeloid metaplasia (MMM), or agnogenic myeloid metaplasia, as it is currently called in the American literature, is a disorder in which a somatic mutation leads a multipotent hematopoietic progenitor cell to acquire a clonal proliferative advantage. This primary event, common to all chronic myeloproliferative disorders (CMDs), is specific for MMM in that it subsequently produces an abnormal population of hematopoietic cells that inappropriately release fibrogenic cytokines and/or growth factors in the bone marrow, precociously invade the blood stream, and colonize extramedullary sites. These biologic hallmarks virtually differentiate MMM from chronic myeloid leukemia, in which the Ph1 chromosome marks the disease, and from polycythemia vera (PV) and essential thrombocythemia (ET), the other so-called Ph1-negative CMDs. The functional derangement of the hematopoietic cell clone also determines the phenotype of the disease, which, from the first report by Heuck 120 years ago,[1] has constantly been described as myelofibrosis, immature myeloid and erythroid cells in the peripheral blood, anisopoikilocytosis with teardrop erythrocytes, and progressive splenomegaly caused by myeloid metaplasia.

MMM is a rare disease. In the most reliable population-based body of data on specific leukemias available in the United Kingdom, the incidence of MMM was estimated to be 0.73 per 100,000 person year in males and 0.40 per 100,000 person year in females.[2] This means an expectation of roughly 230 new cases each year in England and Wales, 330 in Italy, and 1,600 in the United States. The excess of male cases is evident after men reach the age of 50 years, suggesting a possible ''protection'' effect among postmenopausal women or occupational or environmental factors that may act as particular risk factors for males.

It seems natural to classify MMM according to whether it develops idiopathically (primary MMM) or follows another typical CMD (secondary MMM). Secondary MMM accounts for approximately 10% of all cases (personal observation). Myelofibrosis (postpolycythemia MMM) develops in 25% to 50% of patients with PV[3,4] and in 2% to 3% of patients with ET.[5]

From the Laboratory of Medical Informatics, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Pavia, Italy.

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Address reprint requests to Giovanni Barosi, MD, Laboratorio di Informatica Medica, Istituto di Ricovero e Cura a Carattere Scientifico Policlinico S. Matteo, Piazzale Golgi 2, 27100 Pavia, Italy; email barosig@smatteo.pv.it.

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DISTINCTIVE BIOLOGIC FEATURES

Current knowledge about the cellular and molecular pathogenesis of MMM does not allow us to outline a single model that justifies the proliferative advantage of the hematopoietic cells, the disruption of normal bone marrow extracellular texture with fibrosis, and the native extramedullary hematopoiesis. A detailed presentation of the biology of MMM is beyond the scope of this review. The focus of this article is on biologic parameters that may be useful in delineating specific features that make MMM a unique disease in the field of CMDs.

Clonality

MMM has invariably been reported to be a clonal disorder. Its clonal nature has been inferred from isoenzyme expression for glucose-6-phosphate dehydrogenase,[6] variable but not random patterns of chromosomal abnormalities,[7] mutations of the Ras gene family,[7,8] X chromosome inactivation patterns,[9] and loss of heterozygosity.[10] The constancy of clonal hematopoiesis is at variance with other Ph1-negative CMDs that are occasionally reported to be nonclonal.[11,12] Clonality in MMM invariably involves erythroblasts, megakaryocytes, granulocytes, monocytes, and B lymphocytes, documenting that the disorder stems from a pluripotent progenitor. MMM is also unlike other Ph1-negative CMDs, in which the contribution of clonal hematopoiesis in different lineages is variable and in some cases restricted to a single hematopoietic lineage.[12] Clonality in the T-lymphocyte population has been observed in only a fraction of patients with MMM,[13] which suggests that the myeloproliferation originates from a committed progenitor cell with heterogeneity of lymphocyte lineage involvement.

Myeloid Proliferative Advantage

The biologic and molecular mechanisms responsible for the clonal proliferation in MMM are presently unknown. At the cellular level, the proliferative advantage of the mutated clone is documented by the elevated in vitro growth of hematopoietic progenitor cells, by their enhanced sensitivity to hemopoietic growth factors, or by their autologous growth, ie, independent of growth factor stimuli.[14-20] A number of growth factor pathways have been investigated and a variety of anomalies detected; however, most of them are common to other CMDs and affect a limited number of the cases investigated, which suggests that they are acquired abnormalities in the evolution of the neoplastic clone.

Both elevated expression[21] and point mutation[22] of the stem-cell factor (SCF) receptor (c-Kit) in circulating stem cells have been reported. It has been hypothesized that they are the cause of the high sensitivity of myeloid progenitor cells to SCF[23] and contribute to the proliferative advantage of the affected clone. c-Kit is a 145-kd glycoprotein composed of an extracellular domain and a cytoplasmic tyrosine kinase domain connected by a single transmembrane region. The mutated codon 52 described in two patients with MMM[22] is in the molecular domain; its function is to stabilize the SCF binding site, thereby affecting the tertiary structure of the SCF binding site and leading to the enhancement of receptor tyrosine kinase activity.[23]

Deregulation of the basic fibroblast growth factor (b-FGF) pathway in primitive hematopoietic stem cells is hypothesized to be a primary event in the abnormal hematopoiesis of MMM.[24] The FGF family of growth factors, produced by a variety of cells, including hematopoietic and stromal cells, selectively acts on primitive stem-cell growth by binding to high-affinity receptor tyrosine kinases. Compared with normal CD34-positive progenitors, the expression of b-FGF is significantly increased in the CD34-positive cells of MMM patients, and the density of b-FGF type I and type II receptors is significantly augmented.[24] This increased b-FGF expression is in contrast to a decreased expression of the receptor for the transforming growth factor-beta (TGF-β), a negative regulator of hematopoiesis.[24]

The prominent proliferation of abnormal megakaryocytes in the bone marrow and the role megakaryocytes are supposed to play in the genesis of bone marrow fibrosis have focused interest on thrombopoietin (TPO) and its receptor, Mpl, in the pathogenesis of MMM. The best-characterized physiologic effect of TPO seems to be on the proliferation and differentiation of megakaryocyte precursors,[25] but TPO also acts directly on primitive hematopoietic stem cells in vitro,[26] and mice with a deficiency of TPO or its receptor have reduced numbers of both multilineage and committed hematopoietic progenitor cells.[27] Thus, theoretically, deregulation of TPO, the TPO receptor, or the post–receptor signaling pathway system could justify the multilineage involvement of hematopoiesis in MMM.

A truly autonomous megakaryocyte development occurs in MMM that does not result from mutations or deletions in the coding region of the TPO receptor, nor from an autocrine stimulation by TPO.[20] Reduced surface expression of the TPO receptor in the platelets from 13 of 14 patients with MMM, whether measured functionally by unresponsiveness to TPO or immunologically by flow cytometry using an antiserum against the TPO receptor's N-terminal domain, has been reported.[28] This defect, caused by a specific, incompletely processed form of platelet Mpl associated with impaired complex carbohydrate processing,[29] is associated with a subsequent failure to activate the kinase signaling

system, with subsequent loss of phosphorylation of the proteins involved in signal transduction, JAK2 and STAT5.[28] The platelet and megakaryocyte abnormality that causes failure to bind TPO could reflect the independence of the clonal progenitor cells from growth factors that are normally essential, and fits with the finding of elevated levels of serum TPO in patients with MMM,[30] not consistent with the expected effects of increased megakaryocyte/platelet mass.[31] However, the TPO receptor defect is not restricted to patients with MMM; it also occurs in the majority of patients with PV.[28] These results, along with documentation that PV patients acquire the defect during progression of their disease toward splenomegaly and myelofibrosis,[29] could suggest a common pathogenetic mechanism that links PV to MMM.

A reduced expression of the TPO receptor system is difficult to reconcile with animal models of the disease. Chronic exposure to high doses of Mpl ligand (TPO) has been obtained in animals with the use of different approaches, including repeated systemic injections, reconstitution of lethally irradiated mice with hematopoietic cells infected with a retrovirus carrying Mpl ligand cDNA, adenovirus vector delivery, and transgenesis.[32-37] Overexpression of TPO leads to thrombocytosis, megakaryocyte hyperplasia in the spleen and bones, extramedullary hematopoiesis, myelofibrosis, and osteosclerosis. Moreover, the retrovirus MPVL, which carries a truncated Mpl gene, induces erythrocytosis, thrombocytosis, granulocytosis, and splenomegaly in mice.[38] Thus, overexpression of either TPO or TPO receptor in murine models produces many of the clinical features of MMM; a comparison of the different experimental models strongly suggests that the severity of the syndrome is more closely correlated with the level of TPO in the plasma than with the model of delivery. However, caution has been advised in drawing parallels between MMM and genetically manipulated animal models, because reduced expression or function of TPO receptors in MMM patients may produce unanticipated effects in cells that express a variety of other growth factor receptors.[28]

The molecular mechanisms underlying the development of MMM remain obscure. MMM lacks a unique chromosomal rearrangement that flags the site of a gene important for the pathogenesis of the disease. Nevertheless, three cytogenetic defects, namely del(13q), del(20q), and partial trisomy 1q, account for nearly 65% of all abnormalities at diagnosis[39] and suggest that inactivation or loss of tumor suppressor genes may be intimately associated with tumorigenesis in MMM. Deletions or, more rarely, translocations that involve chromosome 13q occur in 25% of cases with an abnormal karyotype and in 5% to 10% of all MMM cases.[39] Heterozygous deletions of the tumor suppressor gene *RB1* (retinoblastoma gene) assigned to 13q14 have been detected in seven (24%) of 29 patients with MMM by fuorescence in situ hydridization using *RB1* and 13q DNA probes.[40] However, in seven cases with deletion of 13q, the *RB1* gene displayed a germline configuration suggesting that 13q deletions in this disorder may affect a tumor suppressor locus distinct from *RB1*[41]; in five other cases, interstitial deletions and a large amount of lost material indicated that more than one suppressor gene may be involved.[42]

Additional genetic and molecular events may lead to progression of the disease toward the final leukemic phase, particularly mutations of the *p53* gene, homozygous deletions of the *p16* gene, and molecular abnormalities involving the *RAS* family of proto-oncogenes.[43,44]

Bone Marrow Fibrosis

Bone marrow fibrosis in MMM is the result of a prominent infiltrate of fibroblasts and coarse bundles of extracellular matrix in the bone marrow created by the release of stimulatory factors from cells derived from the myeloproliferative clone. Fibroblastic proliferation is a secondary event because fibroblasts do not derive from a totipotent hematopoietic stem cell[6] and they display no intrinsic alteration.[45] Fibrotic bone marrow stroma in MMM is characterized by increased deposition of extracellular matrix proteins, which include collagen types I, III, V and VI, hyaluronic acid, the noncollagenous glycoproteins fibronectin, vitronectin and tenascin, and the basement membrane components collagen type IV and laminin.

An array of humoral factors have been hypothesized to be released from the proliferating hematopoietic cells and to be responsible for the increased collagen synthesis by bone marrow fibroblasts seen in MMM. These factors include platelet-derived growth factor (PDGF), b-FGF, platelet factor-4, TGF-β, beta-thromboglobulin, calmodulin, and interleukin (IL)-1.

Two different proliferating cell populations have been hypothesized to be the sources of fibroblast-proliferating factors. Increased content and abnormalities of packaging and secretion of PDGF, platelet factor-4, TGF-β, b-FGF, and calmodulin in megakaryocytes and platelets[46-49] have for a long time linked megakaryocytes to the pathogenesis of myelofibrosis.[45] According to this hypothesis, megakaryocytes are disrupted by their abnormal proliferation and release cytokines in the bone marrow. Although PDGF is a potent mitogen for fibroblasts, it cannot fully explain the pathogenesis of myelofibrosis, for it has little effect on the production of collagen.[50,51] TGF-β release is thought to be pivotal: it is a potent inducer of collagen synthesis by fibroblasts, and it induces the transcription of most of the connective tissue proteins observed in MMM.[52,53] Further-

more, TGF-β is an inducer of new bone[54] and blood vessel formation,[55] properties that might explain the osteosclerosis and angiogenesis that may accompany myelofibrosis.

Recently, the proliferating clonal population of monocytes-macrophages has been implicated in the pathogenesis of myelofibrosis.[56] Monocytes are potential sources of fibrogenic cytokines in that they produce TGF-β, PDGF, and IL-1. In MMM, bone marrow monocytes are increased in number, and macrophage colony-stimulating factor, a cytokine that is implicated in the proliferation and differentiation of macrophages, has been detected in high levels in the sera of patients with MMM.[57] Rameshwar et al[56,58] first demonstrated that high levels of TGF-β and IL-1 were produced by unstimulated MMM monocytes and were associated with an accumulation of their respective mRNAs and that the overproduction of growth factors from monocytes was mediated, at least in part, by protein interaction between the extracelluar matrix and adhesion molecules, particularly CD44. Accordingly, monocytes in contact with extracellular matrix proteins become activated by increased CD25 expression and tyrosine phosphorylation, with concomitant upregulation of intracytoplasmic TGF-β.

The role of monocytes and macrophages in the development of myelofibrosis in MMM may also be inferred from an animal model of osteomyelofibrosis; human TPO cDNA was expressed in mice with various inherited immune deficiency syndromes by using an adenoviral vector construct, and chronic thrombocytosis resulted.[36] Histologically, severe combined immune-deficient mice developed severe osteomyelofibrosis, osteomyelosclerosis, hepatosplenomegaly, and extramedullary hematopoiesis in the liver and lungs; they ultimately developed progressive pancytopenia, anisocytosis, fragmentocytosis, and a lethal wasting syndrome. In contrast, nonobese diabetic, severe combined immune-deficient mice, which demonstrated a similar extent of TPO overexpression and, in addition to the B- and T-cell immune deficiency, harbored defective monocytes and macrophages, did not develop fibrotic changes in the bone marrow. This model leads to the conclusion that functionally normal monocytes and macrophages are indispensable for the development of secondary osteomyelofibrosis.

Circulating Hematopoietic Progenitor Cells and Myeloid Metaplasia

An increased number of circulating hematopoietic precursors, including CD34-positive cells and pluripotent (colony-forming unit [CFU]–granulocyte, erythroid, monocyte, megakaryocyte [GEMM]) and committed (CFU–granulocyte-macrophage [GM], burst-forming unit–erythroid [BFU-E], and CFU-megakaryocyte [MK]) progenitors, have been documented in patients with MMM and other CMDs.[20,59-64] The number of circulating hematopoietic precursors was always reported to be consistently high in patients with MMM, with the mean increase being nine-fold for CFU-GEMM, eight- to13-fold for BFU-E, 37- to 47-fold for CFU-GM, and 167-fold for CFU-MK compared with controls.[59,62] When cells are measured by flow cytometry, the average CD34-positive cell recovery from peripheral blood is 2.3% of the initial number of mononuclear cells, and more than 3×10^6 CD34-positve cells per 10 mL of blood may be obtained[20,65]; this number is higher in patients with MMM than in those with other CMDs.[20,65] This remains in agreement with the general concept that the circulating pool of CD34-positive cells increases along with the proliferative capacity of the individual CMDs, from ET to PV in the early phase, to PV with large spleen, and finally to MMM.[65] Thus, the emergence of hematopoietic cells from the bone marrow constitutes a feature associated with increased myeloid proliferation. Scant knowledge about the physiologic process of cell egression from bone marrow prevents investigators from defining specific features of the proliferating clone that disrupt anchoring of the cell to the bone marrow microenvironment and transmigration into bone marrow capillaries. Patients with MMM have more circulating progenitors than patients with secondary bone marrow fibrosis, such as that of cancer.[60] Therefore, the disruption of the marrow microvascular system induced by fibrosis does not seem to be sufficient to explain the high number of circulating progenitor cells. The documented relationship between the number of circulating WBC precursors and the degree of bone marrow stromal proliferation[66] suggests that increasing bone marrow fibrosis would promote the release of immature cells into the peripheral blood or, alternatively, shift hematopoiesis toward more immature forms.

Myeloid metaplasia, ie, the presence of proliferating hematopoietic cells and their progenies outside the bone marrow, constantly affects the spleen and liver in MMM patients. Activation of stem cells that have lain dormant in the spleen and liver since fetal life has been hypothesized to be the origin of myeloid metaplasia. Under this hypothesis, MMM would recapitulate ontogenesis by a reversion to fetal distribution of hemopoietic activity, with an expansion of hematopoiesis within the central marrow cavity and an extension of hematopoietic tissue to the marrow cavities of long bones and extramedullary sites. However, hematopoiesis in the spleens of adult patients with MMM differs fundamentally from what occurs in fetal life. While the fetal spleen contributes only marginally to hematopoiesis and contains numerous late erythroid precursors but few early erythroid or granulocytic cells, in the spleens of MMM patients, there is abundant hematopoiesis.[67]A more recent

view is that adult extramedullary hematopoiesis originates from a shift of more immature myeloid cells from bone marrow to extramedullary organs; the human spleen and liver filter circulating hematopoietic cells and are permissive of their terminal differentiation only. This so-called filtration theory[68] is supported by the finding of significant differences between the spleen and the bone marrow in regard to the number of immature hematopoietic precursor cells.[69-71]

DISEASE FEATURES

MMM is customarily considered a disease of adults and the elderly. The median age at diagnosis ranges from 54 to 62 years in the most representative series.[72-84] However, approximately 20% of patients are younger than 55 years of age at presentation,[85,86] and childhood cases have been reported.[87-92]

The presenting features of the disease are protean and reflect the disease type, the progression stage at diagnosis, and the age of the patient. In children, the disease commonly pursues an aggressive and invasive fatal course with minimal or no splenomegaly. Because of the extensive bone marrow fibrosis with dysplastic features, MMM in children has been considered a separate variant from that of adults and is called pediatric hyperproliferative myelodysplasia.[90] A familial presentation has been described, and an autosomal recessive model of inheritance has been suggested.[91,92] In one report, familial MMM was associated with multiple hemangiomas.[92]

In most series, the disease picture mainly reflects the population over the age of 60, which represents approximately 70% of patients.[78] At this age, one third of the patients are asymptomatic at diagnosis,[83] and when present, the most common complaints are related to constitutional symptoms, splenomegaly, and anemia. Fever, weight loss, nocturnal sweating, pruritus, and bone pain are the constitutional symptoms that affect 40% of patients at diagnosis or during the course of the disease.[78] Splenomengaly caused by myeloid metaplasia is present in 85% to 100% of patients at diagnosis,[80-83] and it is massive in about 10% of them.[84] In recent years, a trend toward a less florid clinical picture of MMM at presentation has been reported[93]: patients diagnosed before 1987 presented more often with constitutional symptoms and a higher frequency of splenomegaly at diagnosis than have patients diagnosed more recently.

Heterogeneity of the hematologic picture is distinctive of MMM. From 50%[83] to 70%[84] of patients are anemic at diagnosis, and 25% have severe anemia (hemoglobin [Hb] level $<$ 8 g/dL).[84] Normocytic anemia is the rule, and mechanisms include aregenerative, hemodilutional, and hemolytic anemia. Folate deficiency and iron deficiency are rare. The reticulocyte count is increased in most of the patients, but ineffective reticulocytosis is present in many cases. The extent of erythropoiesis, as measured by ferrokinetic studies, ranges from just detectable to increased as much as 10 times normal.[94] Attempts have been made to classify patients according to the expansion of erythropoiesis and its displacement pattern in extra-axial sites.[94] A class of patients with erythroid aplasia and reduced RBC volume has been described with an unfavorable prognostic course.[95-97] A class with expanded erythropoiesis associated with normal or increased RBC volume and a tendency to displace erythropoiesis in extra-axial sites has been diagnosed as having transitional myeloproliferative disorder.[98] In 15% of cases, a polyglobulia is manifest,[84] and if the RBC mass is measured, the percentage of patients with erythrocytosis is higher still but masked by splenomegaly-induced hemodilution.[94] Circulating erythroblasts range from 0% to 20% at diagnosis and may constitute more than half of the nucleated cells in the peripheral blood after splenectomy.[84] WBCs are increased in approximately 50% of cases, and WBC counts exceeding 30×10^9/L are present in 11% of them.[78] About 37% of patients present with thrombocytopenia at diagnosis, and 28% present with thrombocytosis.[78] Thrombocytopenia is usually multifactorial in cause, due to both marrow failure and hypersplenism. In more than 30% of the cases, circulating blast cells are present at diagnosis.[84]

Extramedullary hematopoiesis is the cause of liver enlargement, which is associated with increased levels of plasma alkaline phosphatase. A variety of symptoms may be due to myeloid metaplasia, including acute cardiac tamponade,[99] hematuria,[100] papular skin nodes,[101] pleural effusion,[102] pulmonary failure,[103] and spinal cord compression.[104]

Disruption of the immune response has been reported to be characteristic of MMM among myeloproliferative disorders. Coombs-positive autoimmune hemolytic anemia, nephrotic syndrome, antinuclear antibodies, rheumatoid factor, lupus-type anticoagulant, and hypocomplementemia have all been documented.[105-111] Autoimmune phenomena, such as cutaneous vasculitis, dermatitis resembling Sweet's syndrome, and pyoderma gangrenosum, have also been described.[112-114] These alterations suggest either clonal involvement of the lymphocyte population in the myeloproliferative disorder or secondary activation of the immune system caused by abnormal monocyte-macrophage function. Levels of the plasma-soluble IL-2 receptor were significantly elevated, suggesting T-cell activation.[115]

Bone marrow histologic pictures range from highly cellular with fewer fat cells and a focal increase of reticulin stroma to the absence of normal hematopoiesis with a dense or loose network of reticulin and collagenous fiber. Different grading systems have been proposed; briefly, myelofibrosis is defined as grade 1 if increased cellularity and reticulinic

fibrosis are observed, grade 2 if overall cellularity is decreased and collagenous fibrosis are present, and grade 3 when osteomyelosclerosis is present.[116,117] Megakaryocyte clustering and increased sinusoidal structures are frequent.[69,77] There is limited documentation of histologic progression during the course of the disease, and on sequential studies, a relatively constant pattern has been seen throughout the disease.[68,118] The myelofibrosis progression index, ie, the ratio between time and difference in fiber content density, reveals that the speed of progression is extremely variable.[119] Bony changes that appear radiologically as sclerosis are characteristically seen in half of the patients. The axial skeleton is most frequently involved, and osteolytic lesions are rare.

Young adults, ie, patients 55 years or younger, tend to have less severe anemia, a higher incidence of splenomegaly, a low rate of thrombocytopenia, and a lower frequency of chromosomal abnormalities.[85,86]

DIAGNOSTIC CRITERIA

If analyzed singly, there is no one biologic, clinical, or pathologic characteristic of the disease that can be considered absolutely specific for MMM. Approximately 10% of patients with other CMDs have substantial collagen deposition in their bone marrow[120,121] and immature myeloid cells in their peripheral blood, just as myeloid metaplasia may intervene during the course of any CMD. Moreover, the characteristic lineage proliferation that allows other CMDs to be categorized with simple diagnostic criteria is absent in MMM. This justifies the fact that efforts to propose diagnostic criteria that are widely accepted and used has long been a prime concern of researchers in the field.

The Polycythemia Vera Study Group (PVSG) was first to formalize a diagnostic procedure for MMM. In 1975, Laszlo[122] proposed a cooperative study on MMM aimed at clarifying the pathogenesis and evolution of the disease. He outlined the following criteria for enrolling patients onto the study: myelofibrosis involving more than one third of the sectional area of a bone marrow biopsy, a leukoerythroblastic blood picture, splenomegaly, and the absence of well-established diagnostic criteria for other CMDs (ie, the absence of increased RBC mass or Philadelphia chromosome), with systemic disorders excluded.

Despite the fact that the PVSG was a frequently referenced investigative group (the literature reports more than 280 citations of articles from the PVSG), subsequent authors practically ignored the entire formulation of the definition of MMM as proposed by Laszlo. A literature analysis (MEDLINE) of the last 30 years, aimed at collecting the diagnostic criteria authors used for including patients in clinical studies on MMM, showed very diverging results. Bone marrow fibrosis, a leukoerythroblastic blood picture, and splenomegaly were necessary diagnostic criteria in only 97.2%, 81.5%, and 83.1%, respectively, of the 71 publications examined (personal observation). The absence of the Ph1 chromosome was considered to be a criterion for the diagnosis of MMM in 19.7% of the studies, and a normal or decreased RBC mass was a criterion in only 3% of studies. Moreover, new criteria were explicitly considered, such as the presence of anemia (19% of the studies), myeloid metaplasia (18.7%), abnormal platelet functions (5.5%), hepatomegaly (2.8%), and clusters of megakaryocytes and megakaryoblasts in the bone marrow (1.4%). The absence of monocytosis was also considered (2.8%) to distinguish MMM from chronic myelomonocytic leukemia.

It is easy to hypothesize that the varieties of diagnostic criteria for MMM used in the literature are the consequence of an accumulation of reports dealing with the heterogeneity of the phenotype of the disease. Moreover, MMM falls in the diagnostic context of CMDs and myelodysplastic syndromes (MDSs). CMDs and MDSs became progressively enriched in categories and variants whose spectra of symptoms gradually came to include characteristics of MMM, with transitional myeloproliferative syndrome,[98] MDS with myelofibrosis,[123-125] chronic myelomonocytic leukemia with bone marrow fibrosis,[126] and atypical myeloproliferative disorders[127] being the most common examples.

The need for nosographic boundaries among CMDs and MDSs led to a number of collaborative efforts during the last 20 years to propose diagnostic definitions for PV, ET, MDSs, and atypical chronic myelocytic leukemias.[128-132] As far as MMM is concerned, only in the last few years were two European projects aimed specifically at providing formal diagnostic criteria for the disease.

To distinguish between the morphologic characteristics of thrombocythemic myeloprolifertive disorders and thrombocythemic states in chronic myeloid leukemia and MDS, Thiele et al[133] established a set of relevant criteria for the diagnosis of MMM with special regard to its early stages. They combined accepted clinical characteristics at diagnosis with corresponding histomorphologic findings (the Cologne criteria), with the belief that bone marrow histology is an invaluable aid when attempting to define the different subtypes of myeloproliferative disorders. They proposed an early phase of the disease characterized by no evident bone marrow fibrosis but the presence of biphasic cellular proliferation of megakaryoctes and neutrophils (chronic megakaryocytic granulocytic myelosis)[134] and the typical morphology of megakaryopoiesis. Megakaryocytes mark MMM by their characteristic bizarre shape; the plump lobulation of nuclei and the disturbance of nuclear cytoplasmic matura-

tion create a dysplastic appearance. Diagnosis of this first stage of the disease is facilitated by a high number of platelets, splenomegaly, and the absence of a leukoerythroblastic blood picture. The disease is postulated to evolve progressively toward stages with anemia, a leukoerythroblastic blood picture, myelofibrosis, and osteosclerosis (Table 1).

The Italian Consensus Conference for the Diagnostic Criteria of MMM originated from the Italian Cooperative Group on Myeloproliferative Disorders.[135] The purpose of the work was to develop a definition of MMM according to the paradigm of ''evidence-based medicine'' using the ''consensus'' methodology. The aim of the project was to arrive at diagnostic criteria that would remain valid for the set of patients with CMDs or MDS and to promote these criteria as a standard for patient inclusion in clinical studies. Thirty-seven diagnostic criteria (23 positive and 14 negative) with their diagnostic performance were extracted from the literature or were newly proposed by an 18-member advisory council. A panel of 12 Italian experts was offered the results of the literature review; using a questionnaire, they ranked the necessary and optional diagnostic criteria according to their preferences in order to identify a core set of criteria. Necessary criteria consisted of ''diffuse bone marrow fibrosis'' and ''absence of Philadelphia chromosome or BCR-ABL rearrangement in peripheral-blood cells.'' The six optional criteria in the core set were splenomegaly of any grade, anisopoikilocytosis with teardrop erythrocytes, presence of circulating immature myeloid cells, presence of circulating erythroblasts, presence of clusters of megakaryoblasts and anomalous megakaryocytes in bone marrow sections, and myeloid metaplasia. To establish the definition of the disease, the panel was convened (Bologna, Italy, May 1997) and asked to score the diagnosis of 46 patient profiles as appropriate or not appropriate for MMM, using consensus formation techniques. Considering the experts' consensus as the gold standard, sensitivity and specificity were calculated for each of the 90 possible definitions of the disease obtained through the core set, and the definitions were ranked by kappa statistics. The definition of the disease with the highest final score was as follows (Table 2): diffuse bone marrow fibrosis necessarily present and Philadelphia chromosome or BCR-ABL rearrangement in peripheral-blood cells necessarily absent; any other two of the core set criteria present when splenomegaly is present; and any other four of the core set criteria present when splenomegaly is absent.

As a first formal attempt at constructing a consensus around the diagnostic definition of MMM, the proposal is noteworthy. However, since the project was not designed on how best to investigate patients in order to reveal the presence or absence of a criterion, most of the formulations of the criteria were drawn from the literature and one could note ambiguity in their formulation. Moreover, the authors were not able to provide firm conclusions about the discriminant ability of the definition of MMM with respect to existing defining criteria for PV and ET and to the features usually reported for a diagnosis of MDS with bone marrow fibrosis. It is also possible that general acceptance of this definition would wait for broader confirmation outside the country where it was issued.

Table 1. The Cologne Criteria for the Diagnosis and Staging of MMM

A.	No preceding or allied other subtype of myeloproliferative disorders or MDS.
B.	Splenomegaly (on palpation or > 11 cm on ultrasound).
C.	Thrombocythemia (platelet count $\geq 500 \times 10^9$/L).
D.	Anemia (Hb < 12 g/dL).
E.	Definite leukoerythroblastic blood picture.
F.	Histopathology: Granulocytic plus megakaryocytic myeloproliferation with large, multilobulated nuclei containing megakaryocytes that show abnormal clustering and definitive maturation defects and
	1. No reticulin fibrosis,
	2. Slight reticulin fibrosis,
	3. Marked increase (density) in reticulin fibers or collagen fibrosis, and
	4. Osteosclerosis (endophytic bone formation).

Diagnosis and classification of IMF is acceptable if the following combinations are present:

Stage 1	A + B + C + F_1 is consistent with a hypercellular (prefibrotic) stage clinically simulating ET.
Stage 2	A + B + C + D + F_2 is consistent with early IMF.
Stage 3	A + B + D + F_3 is consistent with manifest IMF.
Stage 4	A + B + D + E + F_{3+4} is consistent with advanced IMF complicated by osteosclerosis (osteomyelosclerosis).

Abbreviation: IMF, idiopathic myelofibrosis.

Table 2. The Italian Criteria for the Diagnosis of MMM

Necessary criteria

A. Diffuse bone marrow fibrosis
B. Absence of Philadelphia chromosome or BCR-ABL rearrangement in peripheral-blood cells

Optional criteria

1. Splenomegaly of any grade
2. Anisopoikilocytosis with teardrop erythrocytes
3. Presence of circulating immature myeloid cells
4. Presence of circulating erythroblasts
5. Presence of clusters of megakaryoblasts and anomalous megakaryocytes in bone marrow sections
6. Myeloid metaplasia

Diagnosis of MMM is acceptable if the following combinations are present:

- The two necessary criteria plus any other two optional criteria when splenomegaly is present; or
- The two necessary criteria plus any other four optional criteria when splenomegaly is absent.

PROGNOSTIC CLASSIFICATION

The course of MMM is highly variable. In the more recent series, median survival time from diagnosis ranges from 3.5 to 5.5 years,[73-83] with an actuarial survival rate at 2 and 5 years of 68% and 40%, respectively.[78] Analysis of the proportion of lives lost because of the disorders, ie, adjusted for the expected mortality of the age- and sex-matched general population, shows an overall reduction of life expectancy[136] of 31%.[80] Progressive marrow failure, transformation into acute nonlymphoblastic leukemia, and portal hypertension are the major causes of death.[75-77,79]

Several clinical and biologic prognostic parameters have been studied with varying and sometimes conflicting results. In almost all the studies, Hb concentration at diagnosis consistently emerged as an important prognostic parameter, but other clinical and hematologic presenting features maintained an independent predictive value for prognosis and were variably used together with anemia for scoring systems. Varki et al[73] revealed that constitutional symptoms associated with anemia and thrombocytopenia were the factors that best predicted poor survival. Hasselbalch[75] designed a prognostic scale based upon Hb level, platelet count, presence of osteomyelosclerosis (as a favorable parameter), and spleen size. Rupoli et al[77] set up a prognostic scoring system using Hb level, presence of normal megakaryocytes, and fever as factors. Njoku et al[137] proposed a score based on Hb and reticulocyte count; Visani et al[76] identified three prognostic subgroups by taking into account the percentage of WBC precursors and Hb. Dupriez et al[78] recently proposed a score (Lille Scoring System) that was able to identify three distinct prognostic groups (Table 3). In the low-risk group (Hb level $>$ 10 g/dL and WBC count between 4×10^9/L and 30×10^9/L), patients had a median survival time of 93 months, whereas those in the intermediate-risk (Hb level $<$ 10 g/dL or WBC count $< 4 \times 10^9$/L or $> 30 \times 10^9$/L) and high-risk (Hb level $<$ 10 g/dL and WBC $< 4 \times 10^9$/L or $> 30 \times 10^9$/L) groups had median survival times of 26 and 13 months, respectively.

Besides anemia, two additional features emerged as being of prime importance in the prognostic classification of the disease: age of the patient at presentation and abnormal karyotype. In prognostic studies performed using the classification and regression tree approach, both Barosi et al[74] and Kvasnicka et al[80] found age to be the most significant parameter for classifying patients. In the former study, a low-risk group (19.7% of the sample) contained patients who had a diagnosis of MMM before the age of 45 and a percentage of circulating immature myeloid cells lower than 24%: the actuarial proportion of patients surviving at 15 years was 100%. In the latter analysis, the incidence of thrombocytopenia in elderly patients ($>$ 70 years) permitted a clear-cut separation of a high-risk group (22.4% of the sample) with a life expectancy of 2.25 years. A subgroup analysis of previously reported patients allowed Morel et al[86] to document that the disease was less frequently aggressive based on the Lille score in patients younger than 55 years of age. The median survival time of young, low-risk patients was 156 months, which is better than the median survival time previously reported for all low-risk patients (93 months). The Cox model identified only one independent covariate, anemia. More recently, in a European collaboration study of 121 patients aged 55 years or younger,[85] the median survival time was 128 months, ie, more than twice that reported in recent comprehensive series of MMM patients. Anemia, presence of constitutional symptoms, and circulating blasts were the three presenting features associated with survival. These prognostic factors allowed separation of young patients into low-risk and high-risk groups. The low-risk group, with none or only one poor prognostic factor, included three quarters of the patients and had a median survival time of more than 14 years; the high-risk group, with two or three poor prognostic factors, contained a quarter of the patients and had a median survival of less than 3 years.

The importance of an abnormal karyotype in the evolution of the disease was first suggested, albeit indirectly, by Besa et al in 1982.[138] Dupriez et al[78] reported that cytogenetics retained prognostic value in their low-risk group: patients with normal karyotype had a median survival time of 112 months, whereas those with an abnormal karyotype had a median survival time of 50 months. A prognostic staging system was recently proposed by Reilly et al[139] that combines age, Hb value, and karyotype.

Five percent to 30% of deaths are due to blast transformation[78,83,84] of granulocytic, granulomonocytic, or megakaryocytic type.[140] Several attempts have been made to identify clinical and laboratory features that predict evolution to blast crisis. Predictors of such an evolution are severe anemia, a high number of immature myeloid cells in the peripheral blood, and a clinical picture of erythroid failure.[78,84] Although no convincing evidence indicates the use of cyto-

Table 3. The Lille Scoring System for Predicting Survival in MMM

No. of Adverse Prognostic Factors*	Risk Group	Median Survival (months)
0	Low	93
1	Intermediate	26
2	High	13

*Adverse prognostic factors were hemoglobin count less than 10 g/dL and WBC count less than 4 or greater than 30×10^9/L.

toxic drugs to be an inducer of blast transformation, splenectomy is a burden because of the increased risk of leukemia.[84]

THERAPY

No medical therapy has proven to have an effect on overall patient survival, justifying the common attitude toward conservative management of patients with MMM. Patients with an intact quality of life and no threatening hematologic deviations, such as erythrocytosis or thrombocytosis, have usually been considered to not need any treatment. Now, ablation of the abnormal hematopoietic clone with high-dose chemotherapy and allogeneic stem-cell transplantation offers a chance to achieve a cure in MMM. Thus, this is the appropriate time to reconsider the general therapeutical approach to the disease.

Allogeneic Stem-Cell Transplantation

Encouraging results with the use of SCT in small series of selected patients, with an apparent cure in some of them, have been reported since 1982.[141-149] However, the small size of these studies precluded an analysis of factors influencing engraftment, the incidence of severe graft-versus-host disease (GVHD), and survival. A recent report of a collaborative study evaluated the results of allogeneic SCT in patients with MMM on a larger scale.[150] The series included 55 patients (39 males and 16 females) from 27 centers worldwide who received an allogeneic SCT between January 1979 and November 1997 for MMM, including patients with a previous history of ET evolving into MMM. Median age at transplantation was 42 years (range, 4 to 53 years), and the median time from diagnosis to transplantation was 21 months. Sixty-four percent of patients received a conditioning regimen that included fractionated or single-dose total-body irradiation. An HLA-matched related donor was used in most cases, whereas in six of 55 cases, the graft was harvested from HLA-mismatched related or three-loci–matched unrelated donors. Hematopoietic recovery was reached in 50 of 55 patients. Factors associated with a shorter time to reach the neutrophil engraftment end point (absolute neutrophil count of at least 0.5×10^9/L) were splenectomy, absence of grade 3 myelofibrosis, and a high number of nucleated cells infused. Splenectomy and the absence of grade 3 myelofibrosis were also factors associated with a shorter time to achieve the platelet recovery end point (platelet count, 50×10^9/L). Five (9.1%) of 55 patients died early after SCT of primary graft failure, secondary graft failure, or transplantation-related death. Among the 50 assessable patients, 22 had grade 0 to 1, 15 had grade 2, and 13 had grade 3 to 4 acute GVHD. Among 44 assessable patients, 27 experienced chronic GVHD. Nineteen patients achieved a complete histo-hematologic remission. Resolution of myelofibrosis occurred between 21 days and 23 months after transplantation. Seven patients showed evidence of relapse that occurred at a median time of 12 months.

Overall, 43.6% of patients died; causes of death were infections, chronic GVHD, acute GVHD, disease progression, solid organ failure, lymphoproliferative disorders, and graft failure. The Kaplan-Meier estimate of survival at 5 years was 49%, with a 57% survival rate for patients who received an unmanipulated HLA-matched related graft ($n = 44$). Nine patients were alive more than 5 years after transplantation. The probability of death occurring before day 100 was 16%. Hb count greater than 10 g/dL at the time of transplantation and the absence of grade 3 myelofibrosis were significantly associated with a better outcome.

Because of the chance for long survival and a probable cure in some patients with SCT, this approach has to be considered for the treatment of younger patients. It seems unlikely that a clinical trial will be held to establish which strategy is better, so inductive reasoning should guide this decision. The survival of patients younger than 55 years old is significantly greater than that of those older than 55, and the characteristics that predict prognosis in young patients are similar to those for older patients.[86] Moreover, the presence of blasts in the peripheral blood or constitutional symptoms are variables that also affect survival.[85] Thus, for asymptomatic patients with no cytogenetic abnormality, no significant cytopenia, and no blasts in the peripheral blood, whose expected median survival is greater than 14 years,[85] it seems difficult to propose allogeneic SCT. On the other hand, patients with two or three of the above prognostic factors can expect a median survival of 33 months.[85] In comparison with the median survival of approximately 60 months provided by allogeneic SCT, transplantation seems to be the treatment of choice if a suitable donor is available. However, patients have to be informed of the high risk of immediate death along with the possibility of cure. The individual patient's time-dependent risk aversion has to be elicited and evaluated before he or she is enrolled in this new therapy.

Treatment of Anemia

Anemia deserves therapeutic consideration when it is symptomatic or progressively worsening. Aregenerative anemia responds to androgens (nandrolone, oxymetholone, fluoxymesterolone, methandrostenolone, and testosterone enanthate) in 50% to 60% of cases, according to the few ad hoc studies in the literature.[138,151] Chromosome abnormalities and severely compromised hematopoiesis were the best predictors of nonresponse.[138]

Recombinant human erythropoietin (rHuEpo) has also been used. Serum erythropoietin levels in patients with MMM are generally adequate for the degree of anemia,[152] and that would make therapy with rHuEpo inadvisable in this disease. Studies on the use of rHuEPO in MMM have been reviewed in a total of 32 patients.[153] Overall, 53% of them responded to rHuEPO treatment but the vast majority of responders were not transfusion-dependent and the doses required to achieve response were from 300 to 1,500 U/kg/wk. Factors predicting response include serum erythropoietin level less than 123 mU/mL, female sex, and none or mild transfusion requirement. In some patients, aggravation of splenomegaly due to stimulation of extramedullary erythropoiesis caused withdrawal of the drug.

Danazol, the vitamin D_3 analog, 1,25-dihydroxycholecalciferol (1,25-$(OH)_2D_3$), immunosuppression with cyclosporine, and corticosteroids have been reported to be effective in individual cases. However, the small size of these studies precludes any conclusion on their role in the improvement of anemia and reduction of the need for transfusions.

Cytotoxic Agents

Peripheral signs of hyperproliferation, such as thrombocytosis, leukocytosis, and progressive symptomatic splenomegaly, are the main indications for treatment with cytostatics. Hydroxyurea is the most commonly used drug. It is an inhibitor of ribonucleotide reductase, and its use in MMM, as in other CMDs, is controversial due to the risk of leukemia. In vitro and in vivo exposure to hydroxyurea is not associated with an increased number of DNA mutations, suggesting low leukemogenic potential.[154] To date, however, its long-term safety is unknown because there are no controlled or randomized studies in this area. The recommended dose is 30 mg/kg body weight given twice weekly, with 500 mg/d as maintenance.[155] Its possible carcinogenic potential becomes important in young people ($<$ 45 years old), who have the longest life expectancy. In these cases, interferon alfa-2b is a valuable alternative to cytostatic therapy. Because interferon alfa preferentially inhibits the proliferation of the megakaryocyte cell line (CFU-Mk),[16] it is particularly appealing for MMM treatment. Hematologic responses have been seen in approximately 50% of assessable patients, usually with a hyperproliferative type of disease, but responses in single cases with pancytopenia and severe anemia have been reported. Spleen reduction has been documented in fewer than 50% of the cases (Table 4).[156-176] A reasonable starting dose is 5×10^6 units subcutaneously three to five times per week. Long-term control can be obtained with a well-tolerated lower dose.[176]

Role of Splenectomy in MMM

A progressively enlarging, painful spleen with severe anemia and/or thrombocytopenia requires a choice between splenectomy and nonsurgical treatment. The decision depends on the trade-off between the risk of and the benefits from the operation, and at this time, no clear guidelines can

Table 4. Studies Reporting the Effects of IFNα in MMM

First Author, Year (ref)	No. of Cases	IFNα Type	Dose (10^6 IU)	Disease Characteristics	Responses*	Effect on Anemia	Spleen Reduction
Single case reports, 1987-1998[156-162]	7	2b	2.2-3.5 × 3/wk	Pancytopenia, anemia, hypoproliferative	7/7	Improvement	4/5
Parmeggiani, 1987[163]	2	2c	3/m²/d	1: Postpolycythemia 1: Hypercellular	0/2	Worsening	2/2
Hasselbalch, 1988[164]	10	2b	3.5 × 3/wk	3: Accelerated 3: Acute	0/10	7/10 Worsening 3/10 Stable	1/10
Seewann, 1988[165]	5	2c	0.5-2/d	Pancytopenia, anemia	1/5	Stable	0/5
Turri, 1989[166]	5	2a	3/d	Various	0/5	Worsening	2/5
Tichelli, 1989[167]	2	2a	3/d	Thrombocytosis	2/2	NR	NR
Gisslinger, 1989[168]	5	2c	25/wk	Thrombocytosis	5/5	NR	NR
Lazzarino, 1989[169]	3	2b	1-4/d	Thrombocytosis	2/3	NR	NR
Barosi, 1990[170]	14	2b	3/d	Hyperproliferative	12/14	Stable	6/9
McCarthy, 1991[171]	8	2b	3 × 3/wk	1: Acute 7: Chronic	0/8	Stable	3/8
Craig, 1991[172]	2	2b	3 × 3/wk	Leukocytosis	2/2	Stable	2/2
Yataganas, 1991[173]	3	2b	3/d	Thrombocytosis	3/3	Stable	0/3
List, 1992[174]	11	2b	1-3/m²/d	Various	NR	Worsening	NR
Cervantes, 1993[175]	4	2b	3/d	Hyperproliferative	2/4	Improvement	2/4
Gilbert, 1998[176]	39	2b	5/d	Hyperproliferative	NR	NR	21/36
Total	120				36/70 (51.4%)		43/89 (48.3%)

Abbreviation: NR, not reported.

*According to the criteria defined by the authors.

be provided to help solve the dilemma. Splenectomy modifies the natural history of the disease, but no trial has provided evidence that survival is modified. Recent single-institutions experiences in Italy[177] and the United States[178] (71 patients and 223 patients, respectively) showed 8.4% to 9% mortality and 31% to 39.3% morbidity. New hemorrhagic or thrombotic complications occurred in 16.9% of surviving patients[177] and were predicted by an age lower than 50, a normal to high platelet count ($> 200 \times 10^9$/L), and huge splenomegaly ($>$ 16 cm from the costal margin). Anemia substantially improved in 45% and 52% of patients at 3 months and 1 year, respectively, and was predicted by severe anemia, low platelet count ($< 100 \times 10^9$/L), or a normal to high WBC count ($> 4 \times 10^9$/L).[177] Postsurgical thrombocytosis of more than 600×10^9/L and more than $1{,}000 \times 10^9$/L was observed in 20.2% and 5.8% of patients, respectively, and was predicted by a platelet count greater than 50×10^9/L.[178] Massive liver enlargement occurred in 24% of patients.[177] An increased frequency of symptomatic or asymptomatic portal or splenic venous thrombosis warrants routine surveillance imaging with ultrasonography.[179,180]

In a recent article describing 549 patients with primary MMM participating in a collaborative study group comprising 13 large hospitals in Italy,[84] splenectomy was reported to be an independent risk for blast transformation. After splenectomy, a progressive increase in circulating mature and immature myeloid cells with massive liver enlargement due to myeloid metaplasia is associated with a progressive increase in blast cells in the peripheral blood and may precede evolution toward blast transformation. The cumulative incidence of blast transformation was 27% in nonsplenectomized patients and 55% in splenectomized patients 12 years after diagnosis. The risk of blast transformation seemed to be independent of factors related to spleen removal assignment. As a matter of fact, the authors used the propensity score technique to demonstrate that patients with the same propensity for splenectomy showed a higher risk for blast transformation on the basis of having undergone splenectomy. This extensive study confirmed the results of other series reporting a high incidence of blast transformation in patients who had undergone splenectomy,[178,181] The reason splenectomy induces blast transformation is not clear. Because splenectomies in both a healthy population[182,183] and animal models[184,185] did not increase the risk of acute leukemia, a direct effect of splenectomy in accelerating preexisting myeloid proliferation must be considered.

The overall median survival period was 2.0 years (range, 0 to 12.9 years) from the time of splenectomy.[178] Age younger than 45, fewer than 10×10^9/L WBCs, and fewer than 50×10^9/L platelets predicted poorer overall survival.[177,178] Survival was generally longer in patients in whom no blast transformation had occurred.[84] The knowledge that splenectomy provides patients with an additional chance for blast transformation and survival reduction, when considered together with their specific clinical profiles, should influence clinicians' judgment about whether patients would benefit from splenectomy.

No data indicate that the use of splenectomy in MMM is generally declining in frequency. The percentage of patients with MMM who underwent splenectomy was 15.8% in the last 10 years in Italy,[84] but the difference among centers is great. The main reasons for splenectomy are symptomatic splenomegaly (59.7% in Italy[84] and 39% in the United States[178]) and transfusion-dependent anemia (36.8% in Italy[84] and 45.3% in the United States[178]). Other indications are portal hypertension and refractory thrombocytopenia.

A palliative role has been suggested for 2-chlorodeoxyadenosine treatment in patients with progressive hepatomegaly or symptomatic thrombocytosis after therapeutic splenectomy.[186] 2-Chlorodeoxyadenosine, a purine nucleoside analog with therapeutic activity in low-grade lymphoproliferative disorders and a potent myelosuppressive effect, administered at 0.05 to 0.1 mg/kg/d for 7 days for one to five treatment cycles, achieved reduction in liver size associated with marked improvement in fatigue and control of thrombocytosis and leukocytosis in seven of nine patients treated. Toxicity was mainly myelosuppression, which was severe in two patients. Likewise, anagrelide, a selective thrombocytopenic agent with United States Food and Drug Administration–approved labeling for the treatment of ET,[187] may have a role in the treatment of thrombocytosis following splenectomy.

For patients who are not candidates because of general contraindications, an alternative to splenectomy is splenic irradiation. Its prominent cytopenic effect calls for low doses of radiation per course. However, the literature reports median doses of radiation ranging from 2.8 Gy[188] to 24 Gy.[189] Splenic irradiation effectively palliates splenic pain and reverses splenomegaly in 93.9% of patients.[190] Fractionation (twice or three time weekly) is more convenient for the patient and is associated with less hematologic toxicity. Significant cytopenia occurs in 43.5% of patients, with life-threatening pancytopenia after a single course of splenic irradiation occurring in 26% and resulting in fatal sepsis or hemorrhage in 13%.[189] The median duration of response is 6 months (range, 1 to 41 months).[187-190] The increased risk of postoperative bleeding in patients who required subsequent splenectomy dictates against splenic irradiation as an alternative to splenectomy in subjects who are otherwise good surgical candidates.

In conclusion, MMM is a rare disease, and a few institutions in each country are leading centers for patient referral and study. Research networks for sharing knowledge on the disease and for organizing clinical and biologic studies are now developing in Europe (http://www.ewg-mpd.home.ml.org). Apart from a few characteristic features, the disease appearance is protean, making its boundaries among the spectrum of myeloproliferative disorders undefined. The need for rigorous, consistent, and feasible criteria for proper diagnosis has led researchers to identify a core set of criteria whose use will help standardize the conduct and reporting of clinical studies and let practitioners decide whether a patient has MMM. The therapy for this disorder continues to be aimed at improving symptoms, and the absence of controlled clinical trials makes treatment essentially empiric. Evidence has now been acquired that allogeneic SCT is effective and offers a realistic chance for cure in younger patients with a suitable donor, and the decision to address patients to SCT is a new challenge for physicians in charge of patients with MMM.

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