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stem cell. It results in abnormalities in red cell, granulocyte, and platelet production in association with marrow fibrosis and extramedullary haematopoiesis. Aetiology Primary myelofibrosis is known to be a clonal disorder caused by acquired genetic mutations in haematopoietic stem cells leading to activation of the JAK/STAT pathway. Many chromosomal abnormal- ities have been found, and in about 58% of cases there is expres- sion of the JAK2 V617F missense mutation typical of polycythaemia vera (see Chapter 22.3.5). Mutations in CALR or MPL are present in approximately 26 and 6% of cases respectively. None of these mu- tations is specific for primary myelofibrosis however, and in 10% of patients no initiating mutation can be identified. Clinical features and prognosis Many patients are asymptomatic at the time of diagnosis, but common presenting manifestations include fatigue, weight loss, night sweats, fever, dyspnoea, and abdominal discomfort due to splenomegaly (which may be massive). The major complications are the consequences of bone marrow failure and extramedullary haematopoiesis, which most commonly occurs in the spleen and liver, but can occur at any site and compromise organ or tissue func- tion. About 20% of patients develop acute myeloid leukaemia as a terminal event. Investigation and diagnosis Anaemia is the most consistent abnormality, with the blood film showing evidence of a leucoerythroblastic reaction (presence of metamyelocytes, myelocytes, promyelocytes, myeloblasts, nucle- ated red cells, and teardrop-shaped red cells) due to extramedullary haematopoiesis. The presence of marrow fibrosis is essential for diagnosis and usually results in the inability to aspirate marrow from a properly placed needle (‘dry tap’). The presence of genetic markers provides supportive diagnostic data. Treatment Treatment is aimed at improving symptoms. Splenomegaly is gen- erally the most distressing complication, and the nonselective JAK2 inhibitor, ruxolitinib, is effective in reducing spleen size and allevi- ating constitutional symptoms in a majority of patients. In addition, it has been shown to improve survival in patients with advanced dis- ease and lower the JAK2 V617F allele burden. Patients with good performance status as well as those with advanced stage disease who have a matched, related donor should be considered for allo- geneic bone marrow transplantation. Other therapies found to be effective include low-dose interferon, low-dose thalidomide and prednisone, low-dose busulfan, hydroxycarbamide, splenectomy, and splenic irradiation. Folic acid supplementation is often given to prevent deficiency in the context of increased folate requirements, and hyperuricaemia should be treated with allopurinol. Introduction Primary myelofibrosis (also called myelofibrosis with myeloid meta- plasia, agnogenic myeloid metaplasia, or primary myelosclerosis) is a chronic myeloproliferative neoplasm, resulting from the ac- quisition of somatic mutations in a multipotent haematopoietic progenitor cell. This leads to abnormalities in red cell, white cell, and platelet production in association with marrow fibrosis and extramedullary haematopoiesis. Although myelofibrosis in asso- ciation with leucoerythroblastosis and splenomegaly are the clin- ical hallmarks of primary myelofibrosis, these abnormalities can also be seen in other chronic myeloproliferative disorders such as polycythaemia vera and chronic myeloid leukaemia, as well as in a variety of benign and malignant disorders that involve the bone marrow (Box 22.3.7.1). Since there is no specific clonal marker for

 primary myelofibrosis, and since many of the disorders listed in Box 22.3.7.1 are responsive to specific therapies not effective in primary myelofibrosis, the diagnosis of this disorder is one of exclusion. Aetiology Primary myelofibrosis is caused by the acquisition of somatic mu- tations in haematopoietic cells. Analysis of glucose-6-phosphate dehydrogenase isoenzyme expression, X-linked gene inactivation patterns in informative women, and a mutation in the N-ras proto- oncogene have established that primary myelofibrosis is a clonal

dis- order with its origin in a pluripotent haematopoietic stem cell. In some patients, T lymphocytes express the same clonal marker as B lympho- cytes and myeloid cells, indicating involvement at the level of the pluri- potent stem cell. Karyotype and comparative genomic hybridization analysis of primary myelofibrosis patients has identified nonrandom abnormalities on multiple chromosomes. The most frequent aber- rations include deletions on 20q, 17q, and 7p; however, deletions on 5q, 11q, 12p, and 13q and gains on 1q and 9p are also common, as is trisomy 8. Next-generation sequencing analysis has identified mul- tiple recurrent somatic mutations in genes located both within these chromosome aberrations as well as outside these regions. Most not- ably, a mutation in the gene for the tyrosine kinase JAK2 (producing a change from valine to phenylalanine at the 617 position (V617F)), which is located on 9p, is observed in approximately 58% of primary myelofibrosis patients. JAK2 V617F is also present in over 95% of polycythaemia vera patients and 59% of essential thrombocytosis patients. This mutation leads to constitutive activation of the tyro- sine kinase receptor, resulting in increased cytokine release and cell proliferation. Recently, somatic insertions or deletions in exon 9 of the calreticulin gene (CALR) on 19p have been found in approxi- mately 26% of essential thrombocytosis and primary myelofibrosis patients, most frequently occurring in patients who do not possess a JAK2 mutation. Mutations in the thrombopoietin receptor MPL oc- curs in approximately 5% of patients. Together, a mutation in one of these three 'driver' genes can be found in approximately 90% of primary myelofibrosis patients and causes activation of the JAK/ STAT signalling pathway. Other frequently mutated genes include ASXL1, TET2, DNMT3A, and EZH2. While the role of each of these mutations in the pathogenesis of disease is not well understood, they are important markers of clonal haematopoiesis in making a diag- nosis of primary myelofibrosis. In addition, patients with primary myelofibrosis tend to have a greater number of somatic mutations than patients with either essential thrombocytosis or polycythaemia vera, supporting their importance in disease progression. Marrow fibroblasts in primary myelofibrosis, in contrast to the haematopoietic stem cells, are polyclonal, suggesting that the marrow fibrosis is a reactive process initiated by expansion of the malignant clone. Marrow collagen is argyrophilic, so that changes in its distri- bution and content can be analysed histochemically by silver staining early in the disease and by Masson’s trichrome staining later on. Under normal circumstances, the connective tissue stroma of the bone marrow is composed of collagen types I, III, IV, and V together with noncollagen proteins such as fibronectin, laminin, vitronectin, and the proteoglycans. Collagen types I, III, and V form a delicate and usually noncontinuous supporting network for haematopoietic cells, while type IV collagen, laminin, and fibronectin are localized in the basement membranes of arteries in a continuous fashion and along marrow sinusoids in a discontinuous fashion. With increasing marrow cellularity, the collagenous supporting network also increases. With myelofibrosis, however, there is both an increase in the collagen network and a change in its physical characteristics. Condensation of the interstitial fibres results in the formation of thick, continuous, and often wavy bundles in association with an increase in reticular or fibroblastic cells. Sinusoidal basement membrane collagen becomes continuous, leading to sinusoidal dilatation and obliteration with an associated capillary neovascularization. The content of basement membrane fibronectin as well as stromal fibronectin and vitronectin also increases. Although best studied in primary myelofibrosis, the types of collagen involved in marrow fibrosis in this condition do not appear to differ from those involved in the marrow fibrosis associated with the other disorders listed in Box 22.3.7.1. The commonality of the types of collagen involved and the simi- larity of the histological process, regardless of disease association, implies that marrow fibrosis per se represents a final common pathway involved in the response to diverse immunological, meta- bolic, toxic, or infectious stimuli

(Box 22.3.7.1). Megakaryocytic hyperplasia, dysplasia, and clustering are characteristic features of primary myelofibrosis. These cells produce cytokines such as platelet-derived growth factor (PDGF) and transforming growth factor-β (TGFβ) that promote fibroblast proliferation, and platelet factor 4 (PF4), which, like TGFβ, inhibits collagenase. These find- ings suggest that inappropriate release of these fibrogenic proteins by dysfunctional megakaryocytes is the stimulus for myelofibrosis. In support of this contention, increased concentrations of PDGF and TGFβ as well as basic fibroblast growth factor have been observed in the platelets and megakaryocytes from primary myelofibrosis patients. Circulating levels of TGFβ are also increased in primary myelofibrosis, as is the urinary excretion of basic fibro- blast growth factor and calmodulin, another potential fibroblast stimulant present in platelets. Finally, TGFβ promotes the syn- thesis of osteoprotegerin, which impairs osteoclast proliferation and promotes osteosclerosis. The observation that thrombopoietin Box 22.3.7.1 Causes of marrow fibrosis Malignant • Acute lymphocytic leukaemia • Acute myeloid leukaemia • Chronic myeloid leukaemia • Hairy cell leukaemia • Primary myelofibrosis • Lymphoma • Plasma cell myeloma • Metastatic carcinoma • Polycythaemia vera • Systemic mastocytosis Nonmalignant • HIV infection • Hyperparathyroidism • Renal osteodystrophy • Systemic lupus erythematosus • Thorium dioxide exposure • Tuberculosis • Vitamin D deficiency

22.3.7 Primary myelofibrosis 5249 overexpression in mice recapitulates the histological features of pri- mary myelofibrosis supports the contention that megakaryocytes are integrally involved in the development of marrow fibrosis in primary myelofibrosis, as does the development of marrow fibrosis in the grey platelet syndrome, in which impaired megakaryocyte α granule synthesis results in release of cytokines and growth factors into the marrow extracellular matrix. Additional distinct histological abnormalities in primary myelofibrosis include increased marrow angiogenesis due to an in- crease in vascular endothelial growth factor production, marrow sinusoidal dilatation, and intravascular haemopoiesis with an in- crease in circulating CD34+ cells. Increased angiogenesis appears to be an early feature of the disease and correlates better with increased marrow cellularity than with marrow fibrosis. The in- crease in circulating CD34+ cells appears to be a consequence of elevations in neutrophil elastase and matrix metalloproteinases with cleavage of the endothelial cell adhesion molecule VCAM- 1 and down-regulation of the chemokine receptor CXCR4 on the CD34+ cells. Recent work has also identified a noncell autonomous contri- bution of the stem cell niche to disease pathogenesis in primary myelofibrosis. Somatic mutations in haemopoietic progenitor cells cause alterations in the bone marrow microenvironment, such as loss of mesenchymal stem cells and Schwann cells that help regulate haematopoietic stem cells. These changes are thought to occur via aberrant cytokine release produced by clonal progenitor cells, and ultimately promote disease progression. Clinical features Although considered to be an uncommon disorder with an inci- dence of approximately 1:100 000 person-years, clinical studies of more than 1000 patients have been reported over the last 50 years. In contrast to the other chronic myeloproliferative disorders, the median age at diagnosis of primary myelofibrosis, 61 years (range 15–94), is much older. Male predominance is the rule in contrast to polycythaemia vera and essential thrombocytosis, and familial clustering occurs in approximately 10% of cases. The presenting manifestations depend on the stage of the illness but are often bland. Many patients are asymptomatic at the time of discovery. Fatigue is the commonest presenting complaint, followed by weight loss, night sweats, fever, dyspnoea, and abdominal discomfort due to spleno- megaly. Hearing loss due to otosclerosis is an interesting but often nonelicited symptom. Easy bruising or bleeding and acute gout or renal stones are other presenting manifestations that are reason- ably common and directly related to the underlying disease process. Rarely, periostitis

may occur. Splenomegaly is present in virtually every patient with primary myelofibrosis at diagnosis. When it is absent, one should consider other causes for the clinical abnormalities. The degree of spleno- megaly varies but is frequently substantial. However, since the rate of splenic enlargement is variable, spleen size cannot be used as an indication of disease duration. Hepatomegaly, invariably of a lesser extent than the splenomegaly, is present initially in approximately 50% of patients and is usually proportional to the degree of spleno- megaly. Lymphadenopathy is uncommon. With substantial spleno- megaly, cachexia may be prominent. Laboratory studies Due to its origin in a multipotent haematopoietic progenitor cell, primary myelofibrosis affects all blood cell types but not in a pre- dictable manner. Anaemia, usually mild, is the most consistent abnormality. Indeed, a normal haemoglobin or haematocrit in the presence of substantial splenomegaly should lead to imme- diate consideration of polycythaemia vera, since the expanded plasma volume associated with splenomegaly can mask a sub- stantial increase in the red cell mass. The leucocyte and platelet counts can be low, normal, or high without reference to spleen size. Inevitably, due to extramedullary haematopoiesis, metamyelocytes, myelocytes, promyelocytes, myeloblasts, and nucleated red cells will be present in the circulation together with the teardrop-shaped red cells characteristic of this situation (Fig. 22.3.7.1). Although this so-called leucoerythroblastic reaction is not specific for pri- mary myelofibrosis, its absence should challenge the clinical im- pression. Abnormalities in liver function tests are not uncommon but are usually mild and most often involve a reduction in serum albumin and an elevation of liver alkaline phosphatase due to extramedullary haematopoiesis, an abnormality that is usually magnified by splenectomy. The lactate dehydrogenase level is usu- ally mildly increased and correlates best with the leucocyte count. Hyperuricaemia is not infrequent. The leucocyte alkaline phos- phatase concentration can be low, normal, or high and cannot be recommended as a diagnostic test. As mentioned, the JAK2 V617F mutation and less commonly CALR or MPL mutations are present in the majority of patients, but their absence does not exclude the diagnosis. Cytogenetic abnormalities include 13q−, 20q−, trisomy 9, trisomy 8, 12p–, and abnormalities of chromosomes 3, 5, 7, and 11. An increase in circulating CD34+ cells is also characteristic but none of these abnormalities is diagnostic for primary myelofibrosis or present in a majority of patients. Perhaps the most intriguing laboratory abnormalities in pri- mary myelofibrosis are those linked to autoreactivity, such as cir- culating immune complexes, complement activation, elevations in Fig. 22.3.7.1 Peripheral smear showing teardrop cells with leucoerythroblastic picture. 

 antinuclear antibody and rheumatoid factor titres, and a positive Coombs' test in the absence of an overt connective tissue disorder. Although marrow fibrosis has been documented in patients with systemic lupus erythematosus, the linkage between autoimmune ab- normalities and marrow fibrosis is unclear. It does, however, provide another therapeutic option as discussed in the following paragraphs. The presence of marrow fibrosis is essential for a diagnosis of pri- mary myelofibrosis and usually results in a 'dry tap' or the inability to aspirate marrow from a properly placed needle. A prefibrotic phase of primary myelofibrosis has been described retrospect- ively. However, given the similarity of the histopathology of poly- cythaemia vera, essential thrombocytosis, and prefibrotic primary myelofibrosis, prospective substantiation of the latter is not possible in the absence of a specific clonal marker for the disease. Even the presence of myelofibrosis, although mandatory, is not in itself sufficient for diagnosis. This is because polycythaemia vera and chronic myeloid leukaemia and other disorders such as hairy- cell leukaemia, myelodysplasia, and acute leukaemia can present with myelofibrosis. Thus, it is

essential to use the appropriate diagnostic tests (cytogenetics, BCR-ABL1 fluorescent in situ hybridization, flow cytometry, and immunohistochemistry) to exclude these and the other disorders listed in Table 22.3.7.1 that can cause myelofibrosis. Marrow cellularity in primary myelofibrosis may be increased with trilineage hyperplasia and erythroblastic and megakaryocytic islands, decreased with scattered areas of hyperplastic marrow embedded in a collagenous matrix, or hypoplastic with in- tense osteomyelosclerosis and residual megakaryocytic islands (Fig. 22.3.7.2). While there is a correlation between the degree of fibrosis and osteosclerosis, there is no correlation between bone marrow histology and disease duration, platelet count, or spleno- megaly; marrow fibrosis does, however, appear to correlate with the leucocyte count. In general, marrow fibrosis and extramedullary haematopoiesis with myeloid metaplasia appear unrelated, and the latter abnormalities cannot be considered as compensation for the former. Increased marrow angiogenesis is a recently recognized feature of primary myelofibrosis that correlates with increased cel- lularity and extramedullary haematopoiesis independently of the marrow fibrosis. Table 22.3.7.1 Three scoring systems for predicting survival in patients with primary myelofibrosis at diagnosis and during the course of the disease Prognostic factor IPSS DIPSS aaDIPSS Score Score Score 0 1 2 0 1 2 0 1 2 Age (years) <65

> 65 <65 65 White cell count × 1000 <25 25 <25 25 <25 25 Haemoglobin (g/litre) 100 <100 ≥100 <100 100 <100 Blood blast cells <1% 1% <1% ≥1% <1% ≥1% Constitutional symptoms No Yes No Yes No Yes aaDIPSS, age-adjusted Dynamic International Prognostic Scoring System; DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System. (b) (a) Fig. 22.3.7.2 (a) Bone marrow biopsy: showing thick, irregular bone trabeculae with new bone formation, and hypercellular marrow with increased megakaryocytes. (b) Bone marrow trephine biopsy: showing thick coarse reticulin fibres (grade 4 fibrosis). Copyright ©2009 American Society of Hematology.

22.3.7 Primary myelofibrosis 5251 In conjunction with the most severe degree of marrow fibrosis, osteosclerosis develops, with characteristic radiographic abnormal- ities. These primarily involve the axial skeleton but can include the skull, with thickening of the bony trabeculae and patchy or coalescent sclerosis. With obliteration of the axial marrow cavities, extension of the marrow into the long bones occurs. Interestingly, the increase in trabecular bone in primary myelofibrosis is not accompanied by an increase in either osteoblastic or osteoclastic activity. This feature distinguishes the osteosclerosis of primary myelofibrosis from that associated with metabolic causes of osteosclerosis. Course and prognosis Primary myelofibrosis is a chronic progressive disorder with a median lifespan (5.5 years) that is much shorter than for poly- cythaemia vera and essential thrombocytosis. However, the het- erogeneity characterizing the initial clinical presentation is also evident with respect to survival, which can range from less than a year to more than 30 years. Death is usually a consequence of bone marrow failure (haemorrhage, anaemia, or infection), trans- formation to acute leukaemia, portal hypertension, heart failure, cachexia, or myeloid metaplasia with organ failure. Retrospective analysis of the adverse prognostic value of presenting manifest- ations has identified a number of factors that may be useful for both prognostic and therapeutic purposes. These include age at onset (>65 years), anaemia

(haemoglobin <100 g/litre), con- stitutional symptoms, leucocytosis (>25 × 109/litre), thrombo- cytopenia, circulating blast cells (≥1%), and certain cytogenetic abnormalities (trisomy 8, 12p–, 5/5q−, 7/7q−, 1(17q), inv(3), 11q23 rearrangement, alone or in combination). A number of scoring systems have been devised for identifying long- and short- term survivors based on the presence of more than one adverse presenting manifestation. Three such scoring systems that are useful in separating patients of any age with myelofibrosis into low- and higher-risk groups with respect to survival are shown in Table 22.3.7.1. With the institution of these scoring systems, risk stratification of primary myelofibrosis has been redefined using a classification similar to that used for MDS. The IPSS is used to stage primary myelofibrosis patients at diagnosis and the DIPSS and age-adjusted DIPSS are used during the course of the disease with the difference being the greater weight accorded to the pres- ence of anaemia not due to a correctable cause or therapy. The DIPSS+ incorporates thrombocytopenia, transfusion number, and cytogenetics. Unfavourable cytogenetics (trisomy 8, 12p–, 5/5q−, 7/7q−, i(17q), inv(3), 11q23 rearrangement, alone or in combin- ation) together with thrombocytopenia are also independent pre- dictors of leukaemic transformation and as such should be applied to the DIPSS and, in particular, to patients classified as low risk since many of these will reclassified on the basis of these additional risk factors to a higher risk group (Table 22.3.7.2). For example, with normal or sole common cytogenetic abnormalities such as +9, 13q−, or 20q−, median survival is 113 months; with more than one cytogenetic abnormality or sole +8, 5/5q−, 7/7q− or less common ones, median survival is 48 months; with complex abnormalities, median survival is 34 months. This has particular implications with respect to bone marrow transplantation since those with high-risk disease are most likely to benefit from trans- plantation. A scoring system incorporating driver mutation status, termed MIPSS, has also been developed. Driver mutation status has also been shown to correlate with clinical course and overall prognosis. Patients with CALR muta- tions tend to have less incidence of anaemia and thrombocytopenia and improved overall survival compared to patients without CALR mutations, while patients without an identifiable CALR, JAK2, or MPL mutation (the so-called ‘triple negative’ cohort) appear to have the worst overall survival. Complications The major complications of primary myelofibrosis are the conse- quences of bone marrow failure and extramedullary haematopoi- esis. Anaemia may be the result of ineffective erythropoiesis, but haemodilution due to an expanded plasma volume associated with splenomegaly, iron deficiency due to gastrointestinal blood loss, folic acid deficiency due to the increased demands of haematopoi- esis, haemolysis due to autoimmune phenomena or hypersplenism, and, rarely, pyridoxine deficiency are also considerations. In some patients, erythropoietin production may be inappropriately low for the degree of anaemia but in this instance haemodilution also needs to be excluded. Red cell survival and splenic sequestration studies can be useful in determining the splenic contribution to anaemia. Hyperuricaemia is a consequence of increased cell turnover and can provoke acute gout or renal stone formation if left un- treated. Splenic enlargement is inevitable and can lead to splenic infarction, malnutrition due to easy satiety, plasma volume ex- pansion, hypersplenism, portal hypertension, splanchnic vein thrombosis, extreme discomfort due to its mass, and eventually cachexia (Fig. 22.3.7.3). Hepatomegaly is associated with spleno- megaly. Impaired hepatic function is usually a consequence of extramedullary haematopoiesis, which can lead to hepatic fibrosis and portal hypertension. Although myeloid metaplasia due to exuberant extramedullary haematopoiesis is most common in the spleen and liver, it can occur at any site and compromise organ or tissue function. For example, peritoneal involvement can lead to ascites; epidural involvement to spinal cord compression; retroperitoneal involvement to obstructive uropathy or portal hypertension; and pulmonary extramedullary haematopoiesis to

pulmonary hypertension., which can lead to sub- stantial cachexia The reason why myeloid metaplasia is more aggres- sive in some patients than in others is unclear. Table 22.3.7.2 Survival in months according to risk status in primary myelofibrosis Risk status IPSS DIPSS aaDIPSS DIPSS+ Low 135 ∞ ∞ 185 Int-1 95 170 106 78 Int-2 48 48 56 35 High 27 18 27 16 aaDIPSS, age-adjusted Dynamic International Prognostic Scoring System; DIPSS, Dynamic International Prognostic Scoring System; IPSS, International Prognostic Scoring System.

 Approximately 20% of patients with primary myelofibrosis de- velop acute leukaemia as a terminal event. Although some clinicians do not distinguish acute leukaemia presenting with myelofibrosis (malignant myelosclerosis) from primary myelofibrosis, they are clinically distinct entities. The extent to which therapeutic interven- tion with potentially mutagenic drugs such as hydroxycarbamide, alkylating agents, or irradiation predisposes patients with primary myelofibrosis to progress to acute leukaemia (as it does in patients with polycythaemia vera or essential thrombocytosis) is unknown. Again for unknown reasons, splenectomy also appears to be a predisposing factor for the development of acute leukaemia. Platelet dysfunction is a common feature of the chronic myeloproliferative disorders and can lead to spontaneous haem- orrhage as well as increased bleeding during surgical procedures. Although abnormalities in platelet morphology, prolongation of the bleeding time, and abnormal platelet aggregation are frequently observed in patients with primary myelofibrosis, no consistent bio- chemical abnormality has been identified and no platelet function test is predictive for the risk of haemorrhage. Therapy There is no specific therapy for primary myelofibrosis. Treatment should be individualized, based on the patient’s IPSS or DIPSS risk group and age. Asymptomatic, low-risk patients without hyperuricaemia or a remedial cause of anaemia require no therapy, although the oral administration of folic acid (1 mg/day) appears reasonable. Anaemia associated with an inappropriately low en- dogenous erythropoietin level (<100 mU/ml) may respond to re- combinant erythropoietin therapy but the hormone can cause an increase in splenomegaly or hepatomegaly. Patients most likely to respond are those with an absent or low transfusion requirement. Prednisone may also be effective if there is evidence of active inflam- mation or autoimmune abnormalities; a role for danazol remains to be established. Hyperuricaemia should be treated with allopur- inol. Asymptomatic leucocytosis or thrombocytosis requires no therapy. Patients less than 65 years of age and an intermediate-2 or high DIPSS score who have a matched donor should be considered for allogeneic bone marrow transplantation. Unfortunately, the best results have been obtained in patients with good prognosis disease and the transplantation-related mortality can be as high as 32% with a 5-year survival of 60%. Recently, reduced-intensity conditioning was found to decrease transplant-related mortality and achieve re- mission rates of more than 70% even in individuals greater than 60 years of age. However, prospective studies will be required to es- tablish the most effective conditioning regimen, the optimal timing for transplantation, and which patients will benefit most from this procedure. Haploidentical transplantation is also under scrutiny. In symptomatic patients in the absence of a suitable bone marrow donor, treatment has been revolutionized by the introduction of the nonselective JAK2 inhibitor, ruxolitinib, which appears to be ef- fective in JAK2 V617F-negative patients, as well as those positive for this mutation. Currently approved for intermediate-1 to -2 and high-risk patients, the drug is effective in alleviating constitutional symptoms and reducing spleen size in the majority of patients. Importantly, significant relief of symptoms can be achieved with only a small reduction in spleen size. In some patients, anaemia is exacer- bated, but is usually transient and can be temporized with transfu- sion. Thrombocytopenia, even if severe, may

also be improved and is not an absolute contraindication to the drug. Improvements in survival have also been documented in higher-risk patients, how- ever, persistent molecular or pathogenic responses do not occur with this treatment. Loss of response after 3–5 years of treatment is common. The effects of ruxolitinib are durable as long as the drug is administered, but will recur when the drug is stopped and thus it should be discontinued by gradual dose reduction. Thalidomide at low doses (50–100 mg/day) in combination with prednisone has proved to be effective in ameliorating anaemia as well as thrombo- cytopenia in approximately 60% of primary myelofibrosis patients, and reducing spleen size in approximately 20%. Lenalidomide has not proved to be more effective than thalidomide in small phase II trials in the absence of del5q. Pegylated interferon-α at low doses is worth considering to reduce splenomegaly, and has been most ef- fective early in the course of the illness, but can cause cytopenias. Newer targeted therapies, such as selective JAK2 inhibitors, or anti- sense oligonucleotides such as the telomerase-inhibiting imetelstat may lead to improved outcomes in the future. Chemotherapeutic agents or irradiation therapy should be used judiciously in the treatment of idiopathic myelofibrosis. Hydroxycarbamide, while easy to use and with a low incidence of acute toxicity, can cause marrow depression. Low-dose alkylating agent therapy has been demonstrated to reduce organomegaly, reverse marrow fibrosis, and improve blood counts in primary myelofibrosis, occasionally in a durable fashion. However, alkylating agents can also cause severe bone marrow depression and are leukaemogenic. Splenomegaly is the most distressing complication of pri- mary myelofibrosis, leading to mechanical discomfort, inanition, splenic infarction, portal and pulmonary hypertension, and blood cell sequestration. Reduction in splenic size can be achieved with ruxolitinib in most patients, but interferon, thalidomide, alkylating agents, hydroxycarbamide, or splenic irradiation are also effective. After ruxolitinib, either thalidomide or interferon are the ini- tial treatments of choice, followed by chemotherapy with either hydroxycarbamide or low-dose busulfan. Splenic irradiation can be effective at alleviating splenic pain and temporarily reducing spleen Fig. 22.3.7.3 Patient with primary myelofibrosis and massive splenomegaly who underwent splenectomy. 

 size. However, its use should be restricted to inoperable patients since there is an unpredictable risk of severe cytopenias as well as an increased risk of haemorrhage, if irradiation precedes splenectomy. Local irradiation is, of course, appropriate for the management of symptomatic extramedullary haematopoiesis in tissues and organs other than the spleen. Splenectomy in primary myelofibrosis is a prodigious pro- cedure, given the large size of the spleen and its vessels, the inevit- able presence of adhesions, the haemorrhagic tendency of primary myelofibrosis patients, and their often poor nutritional status. Evaluation for portal hypertension should precede surgery and, if necessary, parental hyperalimentation should be used to avoid postoperative complications. ε-Aminocaproic acid can be used if bleeding is a problem. Leucocytosis, thrombocytosis, and postoperative hepatic enlarge- ment are the usual consequences of splenectomy, as is elevation of liver alkaline phosphatase. Postoperative splenic and portal vein thrombosis occur in approximately 10% of patients, most often in the first few weeks after surgery and presumably due to the size of the splenic vein remnant. However, there is no correlation between splenic or portal vein thrombosis and the platelet count. Surveillance by ultrasonography or CT may useful in identifying this complica- tion with the intent of administering anticoagulants or thrombolytic agents. For unknown reasons, the incidence of the transformation of primary myelofibrosis to acute leukaemia is increased post splenec- tomy. Postoperative ventral hernia can be a source of distress, par- ticularly in women. Finally, as mentioned earlier, autoimmune phenomena are fea- tures of primary myelofibrosis. Corticosteroids may be beneficial

if autoimmune phenomena are clinically significant, if there are as- sociated constitutional symptoms, and for the amelioration of an- aemia. Tuberculosis was once a frequent complication of primary myelofibrosis and, thus, constitutional symptoms in these patients should not be attributed to the myeloproliferative disease without first excluding an infectious process. FURTHER READING Arranz L, et al. (2014). Neuropathy of haematopoietic stem cell niche is essential for myeloproliferative neoplasms. Nature, 512, 78–81. Brecqueville M, et al. (2014). Array comparative genomic hybridiza- tion and sequencing of 23 genes in 80 patients with myelofibrosis at chronic or acute phase. Haematologica, 99, 37–45. Cervantes F, et al. (2009). New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. Blood. 113, 2895–2901. Chagraoui H, Wendling F, Vainchenker W (2006). Pathogenesis of myelofibrosis with myeloid metaplasia: insight from mouse models. Best Pract Res Clin Haematol, 19, 399–412. Elliott MA, et al. (1998). Splenic irradiation for symptomatic spleno- megaly associated with myelofibrosis with myeloid metaplasia. Br J Haematol, 103, 505–11. Gangat N, et al. (2011). DIPSS Plus: a refined dynamic international prognostic scoring system for primary myelofibrosis that incorp- orates prognostic information from karyotype, platelet count, and transfusion status. J Clin Oncol, 29, 392–7. Glew RH, Wolfgang HH, McIntrye PA (1973). Myeloid metaplasia with myelofibrosis. The clinical spectrum of extramedullary hematopoiesis and tumor formation. Johns Hopkins Med J, 132, 253–70. Hussein K, et al. (2010). International Prognostic Scoring System – in- dependent cytogenetic risk categorization in primary myelofibrosis. Blood, 115, 496–9. Klampfl T, et al. (2013). Somatic mutations of CALR in myeloproliferative neoplasms. N Engl J Med, 369, 2379–90. Kroger N, et al. (2009). Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a pro- spective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. Blood, 114, 5264–70. Kroger N, et al. (2015). Impact of allogeneic stem cell transplant- ation on survival of patients less than 65 years of age with primary myelofibrosis. Blood, 125, 3347. Lundberg P, et al. (2014). Clonal evolution and clinical correlates of somatic mutations in myeloproliferative neoplasms. Blood, 123, 2220–8. McLornan DP, et al. (2012). Allogeneic stem cell transplantation for myelofibrosis. Br J Haematol, 157, 413–25. Mesa R, et al. (2000). Evaluation and clinical correlations of bone marrow angiogenesis in myelofibrosis and myeloid metaplasia. Blood, 96, 3374–80. Mesa R, et al. (2003). A phase 2 trial of combination low-dose thalido- mide and prednisone for the treatment of myelofibrosis with mye- loid metaplasia. Blood, 101, 2534–41. Mesa R, et al. (2006). Palliative goals, patient selection, and periopera- tive platelet management. Cancer, 107, 361–70. Pardanani AD, et al. (2006). MPL515 mutations in myeloproliferative and other myeloid disorders: a study of 1182 patients. Blood, 108, 3472–76. Passamonti F, et al. (2010). A dynamic prognostic model to pre- dict survival in primary myelofibrosis: a study by the IWG-MRT (International Working Group for Myeloproliferative Neoplasms Research and Treatment). Blood, 115, 1703–8. Passamonti F, et al. (2014). Impact of ruxolitinib on the natural his- tory of primary myelofibrosis: a comparison of the DIPSS and the COMFORT-2 cohorts. Blood, 123,1833–5. Rondelli D, et al. (2005). Allogeneic hematopoietic stem-cell trans- plantation with reduced-intensity conditioning in intermediate- or high-risk patients with myelofibrosis with myeloid metaplasia. Blood, 105, 4115. Rumi E, et al. (2014). Clinical effect of driver mutations of JAK2, CALR, or MPL in primary myelofibrosis. Blood, 124, 1062–9. Silver RY, Vandris K, Goldman JJ (2011). Recombinant interferon alpha may retard progression of early primary myelofibrosis: a pre- liminary report. Blood, 1117, 6669–72. Tefferi A, et al. (2008). Low JAK2V617F allele burden in pri- mary myelofibrosis, compared to either a higher allele burden or unmutated status, is associated with inferior overall survival and leukemia-free survival. Leukemia, 22, 756–61. Tefferi A, et al. (2015). A pilot study of the telomerase inhibitor imetelstat for myelofibrosis. N Engl J Med, 373,

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