

Prognostic factors and current practice in treatment of myelofibrosis with myeloid metaplasia: an update anno 2000

F. Cervantes*

Hematology Department, Hospital Clinic, Barcelona, Spain

Summary

Median survival of patients with myelofibrosis with myeloid metaplasia (MMM) ranges from 3.5 to 5 years, but there is a wide variability. The degree of anemia (Hb < 10 g/dL) is the most important prognostic factor, followed by constitutional symptoms and abnormal karyotype. In recent years, different prognostic scoring systems for MMM have been proposed. In some of them three prognostic groups (low, intermediate, and high risk) are recognized, while others recognize a high and a low-risk group only. Median survival of the low-risk group ranges from seven to nine years, while the minority of high-risk patients survive for a median of less than two years. Younger patients with MMM survive longer (median survival above ten years). Among the latter patients, based on Hb value, constitutional symptoms, and blood blast-cell percentage, two prognostic groups can also be identified, with median survival of less than three years and almost 15 years, respectively. Conventional treatment of MMM is mostly palliative and based on cytolytic treatment (usually hydroxyurea), androgen therapy and splenectomy in selected patients. Allogeneic hemopoietic transplant is a therapeutic possibility with the potential for cure in younger patients with bad prognostic features. The role in MMM of newer treatment strategies such as autologous transplantation or the administration of anti-angiogenic drugs such as thalidomide is currently being evaluated. © 2001 Éditions scientifiques et médicales Elsevier SAS

myelofibrosis / myeloid metaplasia / prognostic factor / therapeutic strategy

Résumé – Les facteurs pronostiques et la stratégie courante dans le traitement de la myélofibrose avec métaplasie myéloïde : une mise à jour de l'année 2000.

La médiane de survie des patients atteints de myélofibrose avec métaplasie myéloïde se situe entre 3,5 et 5 ans mais la variabilité est grande. Le degré d'anémie (Hb < 10 g/dL) est le facteur pronostique le plus important suivi par les signes généraux, un caryotype anormal. Récemment différents scores pronostiques ont été proposés. Certains d'entre eux reconnaissent trois groupes pronostiques (haut risque, risque intermédiaire, bas risque) tandis que d'autres ne reconnaissent que deux groupes de risque (élevé ou faible). La médiane de survie du groupe à faible risque varie de sept à neuf ans tandis que le groupe des patients à haut risque, minoritaire, a une médiane de survie de moins de deux ans. Les patients plus jeunes survivent plus longtemps (médiane de survie supérieure à dix ans). Parmi ceux-ci en tenant compte du taux d'Hb, des signes généraux, du pourcentage de blastes sanguins, on peut identifier deux sous groupes : l'un avec une médiane de survie de moins de trois ans et l'autre voisine de 15 ans. Les traitements conventionnels de la myélofibrose avec métaplasie myéloïde sont à visée essentiellement palliative et reposent sur un traitement cytoréducteur (généralement hydroxyurée), une androgénotherapie et la splénectomie dans un groupe de patients sélectionnés. La greffe de moelle allogénique est une option thérapeutique offrant la possibilité de guérison chez les jeunes patients de mauvais pronostic. Le rôle de nouvelles stratégies thérapeutiques comme l'autogreffe de moelle, l'administration de médicaments anti-angiogéniques comme la thalidomide est en cours d'évaluation. © 2001 Éditions scientifiques et médicales Elsevier SAS

métaplasia myéloïde / myélofibrose / facteur pronostique / stratégie thérapeutique

* Correspondence and reprints: F. Cervantes, MD, Hematology Department, Hospital Clínic, Villarroel 170, 08036 Barcelona, Spain.

Table I. Adverse prognostic factors in MMM (multivariate studies).

| Feature | Barosi (1988) n = 137 | Visani (1990) n = 133 | Rupoli (1994) n = 72 | Dupriez (1996) n = 195 | Cervantes (1997) n = 106 | Reilly (1997) n = 106 |
|---------------------------------|--|-----------------------------|----------------------------|------------------------------|--------------------------------|-----------------------------|
| Older age | + | – | – | + | – | – |
| Male sex | – | – | – | + | – | – |
| Constitutional symptoms | | | + | + | + | |
| Spleen or liver size | – | – | – | – | – | – |
| Hb < 10 g/dL | + | + | + | + | + | + |
| WBC count | – | + | – | + | – | + |
| High % blood myeloid precursors | + | + | – | – | – | |
| Blood blasts | | | | + | + | – |
| Thrombocytopenia | – | – | – | – | – | + |
| Abnormal karyotype | | | | + | | + |
| Others | Erythroid iron turnover Marrow “aplastic” pattern | | | | | |

* high; ** low or high.

Myelofibrosis with myeloid metaplasia (MMM), also known as idiopathic myelofibrosis or agnogenic myeloid metaplasia, is an infrequent chronic myeloproliferative disorder characterized by bone marrow fibrosis and extramedullary hemopoiesis, usually accompanied by splenomegaly and leucoerythroblastic picture in the peripheral blood [1]. In recent years, increasing attention is being paid to the study of prognostic factors in MMM [2–11], and several proposals of prognostic stratification of these patients have been published [4, 6, 7, 9–11]. On the other hand, the recognition of the fact that the treatment modalities currently available for MMM are mostly palliative and do not prolong significantly the patients' survival has stimulated the interest for the design of newer treatment strategies aimed at modifying the evolutive course of MMM and, ideally, curing the disease, with this being specially so in the minority of younger patients [12].

The present review briefly summarizes the current status on prognostic factors and prognostic classification of MMM, as well as the current practice and future trends in the treatment of the disease.

SURVIVAL AND PROGNOSIS OF MMM

Median survival of MMM patients ranges in modern series from 3.5 to 5 years [4–10]. However, there is a wide variability, since some patients die after one or two years from diagnosis whereas others survive for even decades. This fact has stimulated the interest for the identification of those variables that, when present at diagnosis, allow

to predict the survival of the patients. The results of the main prognostic studies published in the last 12 years are summarized in *table I*. As can be observed, the degree of anemia is the initial variable most consistently associated with the prognosis of MMM, with a Hb < 10 g/dL being the main unfavorable prognostic factor in all studies [4–11]. Two other features, namely, constitutional symptoms (fever, night sweats, weight loss) [7, 9, 11, 13] and abnormal karyotype [5, 10], have been found to be associated with an adverse prognosis in all studies in which they have been analyzed. Other variables, such as older age [4, 7, 10], low or high leucocyte counts [7], high percentages of immature myeloid precursors in blood [4, 6, 8], thrombocytopenia [10], presence of blood blast cells [7, 9, 11], and iron erythrokinetic pattern [4], have been linked to a bad prognosis in some studies. On the contrary, prognostic significance has been rarely observed for patients' gender, spleen and liver size, and bone marrow histologic stage of MMM.

PROGNOSTIC SCORING SYSTEMS OF MMM

Based on the above mentioned prognostic factors, a number of scoring systems for MMM have been proposed, aimed at identifying at presentation subgroups of patients with a different prognosis [4, 6–10]. *Table II* summarizes the main attempts of prognostic classification of MMM published in the last decade [6, 7, 9, 10], selected according to the following prerequisites: a) they were derived from series including more than one

Table II. Prognostic scoring systems for MMM.

| <i>Author (year)</i> | <i>No. of patients</i> | <i>Prognostic factors</i> | <i>Prognostic groups</i> | <i>Median srv of groups (mos.)</i> |
|----------------------|------------------------|--|--------------------------|------------------------------------|
| Visani (1990) | 133 | Hb < 10 g/dL Blood myeloid precursors > 10% | 3 | 81/39/31 |
| Dupriez (1996) | 195 | Hb < 10 g/dL WBC < 4 or > 30 × 10 ⁹ /L | 3 | 93/26/13 |
| Cervantes (1997) | 106 | Hb < 10 g/dL Constitutional symptoms Blood blasts ≥ 1% | 2 | 99/21 |
| Reilly (1997) | 106 | Hb < 10 g/dL Age > 68 yrs. Abnormal karyotype | 2 | 108/16 |

Studies considered: no. patients > 100; multivariate analysis; exclusion of post-PV cases; "prefibrotic" IM not included.

hundred patients, b) they were based on multivariate statistical methods, and c) the series analyzed did not include patients with either post-polycythemic myelofibrosis or the so-called "pre-fibrotic" myelofibrosis. In all studies a Hb < 10 g/dL was the main unfavorable prognostic factor, while the other factors varied. As it can be observed, in some of the studies three risk groups were considered [6, 7], whereas in others two risk groups were identified [9, 10]. Median survival of the low-risk group ranged from seven to nine years, and median survival for patients in the high-risk group (which included a minority of the patients) was less than two years.

More recently, attention has focused on the prognosis of younger patients with MMM, in whom more intensive therapeutic approaches seem more justified. Thus, in a recent study of patients 55-years old or younger from four European institutions [11], it was seen that such patients represented a quarter of the overall MMM population and that they had a median survival about ten years. In these younger patients, the initial factors associated with a bad prognosis were a Hb < 10 g/dL, constitutional symptoms and the presence of blasts in the peripheral blood. Based on the above three variables, two prognostic groups were identified: a "low-risk" group, including patients with none or one of the bad prognostic factors, and a "high-risk" group, integrated by patients with two or the three bad prognosis factors. The "low-risk" group encompassed three quarters of the overall patients and had a median survival exceeding 14 years, whereas the "high-risk" group included a quarter of the patients, with a median survival of less than three years.

TREATMENT

Despite progress in the understanding of the pathogenesis of MMM, the disease remains incurable, perhaps with the only exception of a few young patients. Because of this, when considering treatment of MMM, the first premise to take into account is that in the vast majority of patients therapy is merely palliative and primarily aimed at alleviation of symptoms and improvement in quality of life, with no significant effect on the prolongation of survival. The marked heterogeneity of the MMM would be the second premise, since it makes necessary to adjust the treatment to the patients' characteristics.

Current practice in the treatment of MMM

In clinical practice, most MMM patients can be included into the following three categories: a) asymptomatic patients, b) patients with a more "proliferative" disease and c) patients with anemia as the main problem. It is generally agreed that in asymptomatic patients with stable disease and lack of other factors such as thrombocytosis, marked leucocytosis or severe thrombocytopenia, a wait-and-see approach is a reasonable option. In these patients the start of treatment is delayed until significant changes in the clinical or hematological situation are observed upon periodic observation.

For patients with a more "proliferative" form of MMM, as manifested by the presence of thrombocytosis and/or marked leucocytosis, marked and symptomatic splenomegaly, and often constitutional symptoms, there is an indication for cytolytic treatment. In such cases hydroxyurea is the first choice [14], whereas busulfan or 6-mercaptopurine can be also useful.

Anemia represents the main clinical problem for a high proportion of MMM patients. In these cases it is mandatory to rule out treatable causes of the anemia, such as iron or, more rarely, folate deficiency. The same applies to autoimmune hemolysis. In the vast majority of MMM patients in whom the anemia can not be attributed to the above mentioned causes, androgen therapy (either oxymetholone or danazol) is the treatment of choice [15, 16]. In order to identify responsive patients, the latter treatment should be administered at adequate doses (oxymetholone, 100 to 150 mg/day; danazol, 600 to 800 mg/day) for at least six months, with careful monitoring of liver function tests as well as periodic ultrasound imaging surveillance to detect the possible appearance of therapy-induced liver tumors. Thirty to 40% of MMM patients in this clinical category show a response to androgen therapy, with a decrease and, in some cases, even temporary cessation of the transfusion requirement. In this sense, it has been pointed out that patients with a normal karyotype have the higher chance of obtaining a favorable response to androgen therapy [15]. A few patients with anemia unresponsive to androgens may respond to a trial of steroids (prednisone, at an initial dose of 1 mg/kg/day for one month, with progressive tapering to a maintenance dose of 30 mg every other day), with this being specially true for patients with "immunological" features. To avoid iron overload, chelation therapy should be considered in patients with frequent transfusion requirement.

Some MMM patients may obtain benefit from splenectomy. This surgical procedure has, however, a number of disadvantages, namely, a high morbidity rate derived from bleeding, infection and thrombosis, a 10% mortality from the same origin, the possible development of hepatic failure due to post-splenectomy massive myeloid metaplasia, of the liver, and an increased rate of transformation to acute leukemia [17, 18]. Splenectomy is also contraindicated in patients with thrombocytosis. Because of the above risks, splenectomy should be strictly restricted to patients with marked, symptomatic splenomegaly unresponsive to conventional therapy, severe and refractory cytopenia, uncontrollable hemolysis or MMM-derived portal hypertension. For patients in the above situations who are poor candidates to surgery, low dose splenic irradiation can be an alternative. It has to be noted, however, that this procedure is associated with frequent side effects (mainly, worsening of the cytopenias), and that its effect on the spleen size usually lasts for only a few months. On the other hand, radiation therapy has a clear role in the palliation of severe splenic infarct pain and in the treatment of extramedullary hemopoiesis affecting vital organs [19].

Newer drugs

In the last decade several "antifibrosing" agents, such as colchicine, D-penicillamin and 1,25-dihydroxy-vitamin.

D₃, were introduced in the therapy of MMM [20, 21]. However, in clinical practice the results have been disappointing, and these drugs are no longer used in MMM.

Following the favorable results achieved in chronic myeloid leukemia with alaphainterferon, this drug has also been used in MMM. However, in addition to the poor tolerance observed in many of these generally old patients, the available results indicate that the role of this agent in MMM would be limited to a minority of patients. Thus, interferon usually decreases the leucocytosis and the thrombocytosis, but its effect on the reduction of the splenomegaly is less frequently observed, whereas the drug rarely improves the anemia [22].

Human recombinant erythropoietin (rHuEPO) is usually ineffective in the treatment of the anemia of MMM [23]. This is probably related to the fact that the vast majority of MMM patients have increased serum EPO levels [24]. Because of this, rHuEPO should be restricted exclusively to the few patients with anemia and low serum EPO levels.

Other drugs such as suramin, an inhibitor of the transforming growth factor B activity [25], or the purine analog 2'chlorodeoxyadenosine are mostly ineffective in MMM [26]. On its turn, cyclosporin A can be occasionally useful in patients with refractory anemia [27]. Finally, anagrelide, a quinazoline derivative, can be effective as a treatment for thrombocytosis in MMM [28].

Allogeneic stem cell transplantation (allo-SCT)

The experience with allo-SCT in young MMM patients is still limited, due to the low frequency of such patients in the overall MMM population. Guardiola et al. recently reported the results of a retrospective study of allo-SCT in 55 patients younger than 55 years transplanted in 28 centers worldwide [12]. Graft failure approached 10% of patients, with the lack of previous splenectomy and the presence of osteosclerosis at transplant being the factors adversely influencing on engraftment. One-year transplant-related mortality was 27% (22% for patients receiving an unmanipulated HLA-matched related transplant). Five-year probability of survival was 47%, with Hb ≤ 10 g/dL and osteosclerosis being the factors negatively influencing the outcome. Finally, the 5-year probability of treatment failure was 36%, with older age, presence of a cytogenetic abnormality at transplant and absence of grade I graft-versus-host disease being the predictors of treatment failure. Although a more prolonged follow-up is required, it appears that a proportion of young MMM patients might be cured by allo-SCT. However, the above results should be evaluated in the light of our current knowledge on prognostic factors in younger patients with MMM. Thus, allo-SCT appears as the option of choice for high-risk patients, but the decision is more difficult in low-risk patients, taking into account the

relatively high peritransplant mortality and the expected long survival of such patients. Because of this, for these latter patients a wait-and-see approach, delaying transplantation until the appearance of bad prognosis features, is probably the best option.

FUTURE TRENDS

It is now clear that the results of any future treatment for MMM should be evaluated on the basis of the patients' prognostic factors. There is also a need for the introduction of newer drugs in the treatment of MMM and, in this context, anti-angiogenic drugs currently appear as the next candidates. For younger patients with bad prognostic features and no HLA-compatible donor other intensive strategies should be developed. In this sense, autologous SCT might be an alternative, although non-eradicated. Additionally, in patients from 55 to 70 years and bad prognosis features, whose median survival is less than two years, non-myeloablative transplantation strategies could be explored.

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