

Response criteria for myelofibrosis with myeloid metaplasia: results of an initiative of the European Myelofibrosis Network (EUMNET)

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The European Myelofibrosis Network (EUM-NET), a European research network on myelofibrosis with myeloid metaplasia (MMM), has developed a definition of response for the disease by using clinicohematologic, histologic, and cytogenetic criteria. A core set of 5 clinicohematologic criteria was selected out of 9 candidates on the basis of their sensitivity to change measured in 196 patients treated either during clinical trials or routine clinical practice. A consensus panel of 16 international experts was convened and asked to score the level of response in 104 patient profiles as major, moderate, minor, or no response according to changes of the clinicohematologic criteria. Using the experts' consensus as the gold standard, the performance of 100 possible definitions of response was evaluated. Criteria for major or moderate clinicohematologic response were determined to be changes in hemoglobin (Hb) and spleen size and the presence of constitutional symptoms, while changes in platelet count and white blood cell (WBC) count served as complementary criteria and were of value for defining minor responses. A histologic response was defined by changes in bone marrow fibrosis and cellularity grades. The combined use of these response definitions should help standardize the design and reporting of future clinical studies in MMM. (Blood. 2005;106:2849-2853)

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Introduction

Myelofibrosis with myeloid metaplasia (MMM) is a clonal disorder of hematopoiesis categorized in the spectrum of chronic myeloproliferative diseases (CMPDs).^{1,2} The need to unequivocally distinguish patients with MMM from those with other CMPDs has led ad hoc committees to develop diagnostic criteria.^{3,4}

The responses of MMM to therapies, in terms of improved well-being and survival, have to date been evaluated by separately analyzing single clinical, hematologic, or histologic parameters and, as a result, different definitions of response have been proposed.⁵⁻¹¹ There is, therefore, a pressing need for the development of standardized criteria for monitoring and assessing treatment responses, especially for the conduct of clinical research and for comparing the outcome of different clinical trials.

Because standard therapies have not been shown to prolong the overall survival of patients with MMM, the current approach is a conservative one aimed at palliation of anemia, systemic symptoms, and symptomatic splenomegaly. However, new therapies are now available that may affect the natural course of the disease.⁸⁻¹⁰ Moreover, ablation of the abnormal hematopoietic clone with high-dose chemotherapy and allogeneic stem cell transplantation offers a

chance to achieve a cure in MMM.¹¹ Thus, assessment of the response should reflect the specific aims of the treatment, and responses should be graded for both palliative and disease-modifying therapies.

Perceiving the need for the development of rigorous, consistent, and feasible criteria for the response assessment of patients with MMM, European investigators funded by a European Community Concerted Action (European Myelofibrosis Network [EUMNET]) grant collaborated to define the quality and degree of response in MMM. The final goal was to develop a definition of response that would be applicable to future clinical studies as well as in routine clinical practice. This report represents the recommendations from the EUMNET working group and from international experts who participated in the final consensus conferences (CCs).

Patients, materials, and methods

The EUMNET project's response criteria were developed by using a multistep process based on a modified National Institutes of Health (NIH) approach.¹² An 18-member advisory board (AB) constituted in November

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2002 was composed of experienced clinicians and pathologists and was chaired by 3 clinicians with clinical epidemiology expertise. The objectives of the AB were to define the aims of the project, to frame the operative context, to select the members of the CC panels, and to organize the consensus development process aimed at defining the response definitions.

After the initial meetings, the AB agreed on the aim of the project: "to develop a definition of response to treatment in patients with MMM for the clinico-hematological, histological and cytogenetic categories" (Table 1).

Clinicohematologic definition of response

A questionnaire was mailed to all members of the AB asking them to suggest candidate criteria for use in the definition of clinicohematologic response and, in a second questionnaire, to rank the top 9 choices among candidate criteria. All the questionnaires were returned, and the candidate criteria were ranked according to their priority votes, with the 9 criteria that ranked highest forming the preliminary core set of criteria.

The validity of the clinicohematologic criteria as sensitive and specific tools to measure response to treatments was tested in 196 patients reported from 9 cooperative institutions. Many of the patients had been included in prospective therapeutic trials evaluating experimental agents, including standard-dose thalidomide, low-dose thalidomide, pegilated interferon, and imatinib. The remaining patients had been treated with hydroxyurea under current clinical practice. In all the cases, the clinical information available at the start of treatment allowed classification according to the Dupriez prognostic score.13 The median age was 56 years (range, 24 to 72 years), and 107 patients were men. The 9 criteria of the core set were monitored regularly and, to allow comparability, week 24 was chosen for the final analysis. Sensitivity to change of the noncategorical parameters was evaluated using the standardized response mean (SRM).¹⁴ The difference between the values of the criteria obtained at the first and last visit was determined. SRM was calculated as the ratio between the mean and the standard deviation of the difference, with levels above 0.8 denoting high sensitivity to change.¹⁴ The strength of association of the changes during therapy of each parameter was also measured by the correlation statistics.

Based on the results of the sensitivity to change analysis, the AB proposed a final core of 5 criteria and for each of these criteria proposed a definition of response (complete or partial) and of progression.

Five international scientists were asked to join the AB to form an expert panel for the consensus conference (CC). The panel was composed of experts in clinical medicine, clinical research, pathology, outcomes/health services research, and medical decision-making. The clinical experts were from the fields of hematology and medical oncology, and both academic and hospital representatives were included. The panelists were provided with a booklet that summarized the goals of the project and the results of the questionnaire phases. The statistical performance was included for all 5 criteria of the final core set.

The CC was held in Vienna on October 18-19, 2004. The meeting was attended by the members of the CC panel with the assistance of 3 members of the AB (G.B., M.M., N.L.L.). The overall goal of the meeting was to decide on the definition of clinicohematologic response based on the 5 core criteria using a combination of statistical and consensus formation techniques. Existing databases were exploited to build 104 patient profiles in which the absolute values at the start and at the end of treatment were shown for each criterion. The patient profiles were presented to conference

	Table 1	I. Ca	tegories	of res	ponse
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- 1. Clinicohematologic response
- 2. Histologic bone marrow response
- 3. Cytogenetic response

These categories should be applied to patients with MMM (both idiopathic and post-polycythemia vera [post-PV] or post-essential thrombocythemia [post-ET] myelofibrosis) receiving both palliative and disease-modifying therapies. The 3 categories of response should be used in a cumulative sequential manner starting from the clinicohematologic response (thus representing the minimal set of criteria to be evaluated for assessing response). The decision to use a composite definition of response (clinicohematologic and histologic response; or clinicohematologic, histologic, and cytogenetic response) will depend on the goal of the therapy. attendees and, using the nominal group technique,¹⁵ participants at the CC were asked to individually rate each of the patients as either a responder or nonresponder as well as to choose the category of response as major, moderate, minimal, or no response. The moderator asked each member how she/he had voted on each profile. If an 80% consensus was not achieved, the patient profile was discussed in round-robin fashion and a second vote taken. If an 80% consensus was still not attained, the patient profile was declared uninterpretable and was not considered further. By using combinations of the core criteria, the AB developed for testing a set of 100 sound definitions of clinicohematologic response for MMM. The ability of the 100 candidate definitions to classify individual patients as having major, moderate, minor, or no response was evaluated, and the agreement between the classification based on the definitions and the consensus of the physicians was assessed. Using the physicians' consensus judgment as the gold standard, percent false positive and false negative rates, χ^2 , sensitivity, and specificity for each of the 100 definitions of response for MMM were calculated. Only patient profiles for which physician consensus was achieved were used. Definitions of response showing either a sensitivity or specificity of less than 80% were eliminated from further consideration. We used the κ statistic as an additional measure of agreement between the physicians' evaluation¹⁶ and the definitions: κ values 0.7 or above were considered to be evidence of agreement.

Definition of histologic response

The definition of histologic response was dependent on grading of bone marrow fibrosis and bone marrow cellularity. A CC was organized in Palermo on October 28-31, 2004. The meeting was attended by 2 pathologists of the AB and 11 European hematopathologists. All the 13 experts reviewed, using a multiheaded microscope, more than 150 trephine biopsy samples from various medical institutions. Specimens included different lesions but were predominantly cases of CMPDs before and after therapy. Assessment of parameters was made by using a multiple eyepiece microscope, and grading was performed in an independent fashion by each participant. Consensus was assumed when at least 11 of the 13 pathologists achieved the same scoring.

Definition of cytogenetic response

The AB of this project discussed and decided to adopt the cytogenetic response criteria already published for myelodysplastic syndromes.¹⁷

Results

Selection of the criteria and of the best definition for the clinicohematologic response

The AB listed 16 criteria to be included as candidate criteria for the clinicohematologic response assessment in patients with MMM. The 9 criteria with the highest preference rate from the questionnaire as the core set of criteria to use during therapy evaluation were hemoglobin (Hb) (score 130), spleen size (score 100), platelet count (score 84), absolute number of CD34⁺ cells in peripheral blood (score 76), white blood cell (WBC) count (score 70), percentage of blasts in peripheral blood (score 69), serum lactate dehydrogenase (LDH) level (score 60), quality of life (score 54), and constitutional symptoms (score 50).

The Dupriez prognostic score for the 196 patients enrolled into the study of sensitivity to change of the core set of parameters was low for 67 patients, intermediate for 103 patients, and high for 26 patients. While all 196 patients included in the protocol had repeated evaluation of Hb, spleen size, WBC count, and platelet count, only 115 of 196 had repeated enumeration of CD34⁺ cells in peripheral blood and 96 of 196 had repeated measurement of LDH and percentage of blasts in peripheral blood. By considering the

Table 2. Performance of the candidate clinicohematologic criteria

Criterion	Pretreatment value	No. of patients	SRM
Hb level	< 100 g/L	86	0.67
Spleen size	> 10 cm below the left costal margin	89	0.58
Platelet count	< 150 $ imes$ 10 ⁹ /L	71	0.40
CD34 count	> 100 $ imes$ 10 ⁶ /L	67	0.39
WBC count	$>$ 25 $ imes$ 10 9 /L	20	0.09
Blasts in peripheral blood	> 5%	32	0.17
LDH	> 3 times normal	14	0.56

SRM indicates standardized response mean.

whole population of patients, no parameter had an SRM of 0.8 or more, and SRM was more than 0.3 for Hb, spleen size, and CD34⁺-cell number in peripheral blood. However, in specific patient subsets (Table 2), SRM was more than 0.5 for Hb, LDH, and spleen size. Regression analysis indicated a significant association (P < .01) between changes of spleen size and of number of blasts and between changes in CD34+ cells in peripheral blood and LDH. Face validity (ie, a subjective judgment of clinical appropriateness) and content validity (ie, a subjective judgment of the relevance of the individual candidate criteria) were analyzed and discussed by the AB. Taking into account SRM and validity judgments, the final core set to be used in the clinicohematologic response included 5 of the 9 criteria (Table 3). Quality of life measures, CD34⁺-cell count in peripheral blood, and serum LDH were recommended as independent parameters to be evaluated during clinical trials but not to be included in the response definition.

During the Vienna CC, the 16 panel members, using the patient profiles, scored 23 of the 84 patients as having a major

Table 3. Def	inition of	f response	for each	core clin	icohemato	logic	criterio
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response, 22 as having a moderate response, 9 as having a minimal response, 17 as having no response, and 13 as uninterpretable. Eight of the 100 definitions of response showed χ^2 more than 10. The definitions of response that scored highest are reported in Table 4.

Definition of histologic response

The results of the Palermo meeting for grading of bone marrow fibrosis and assessment of cellularity are reported in detail elsewhere.¹⁸ In summary, it was agreed that the basic requirement for assessment of cellularity is a representative biopsy, defined as an artifact-free, nontangential sample at least 1.5 cm long. In addition, the optimal thickness of the paraffin sections should be 3 to 4 μ m, and the cellularity should be documented in relation to age and with respect to normally occurring ranges (Table 5). Quantity and quality (reticulin/collagen) of the fiber content should be determined only in areas of hematopoiesis by using a scoring system comprising 4 grades (Table 6). Recommendations for applying the scoring system included firstly to assess the quality of the reticulin stain by detection of normal staining in vessel walls as internal controls. Furthermore, lymphoid nodules and vessels as well as fibers framing adipocytes should be disregarded. Finally, areas of prominent scleredema (ie, gelatinous edema showing a tendency to develop a discrete reticulin fibrosis) and/or scarring should be included in the overall grading of myelofibrosis.

The AB decided that a histologic response should be defined both for cellularity and for bone marrow fibrosis and that grading of the response should reflect the grading difference between beginning and end of therapy.

Criterion	Complete response	Partial response	Progression
Hemoglobin (Hb) level	$\label{eq:bound} \begin{split} Hb &\geq 120 \text{ g/L for patients with Hb} < 100 \text{ g/L; or} \\ achievement of transfusion independence, \\ with stable Hb > 110 \text{ g/L, for RBC} \\ transfusion-dependent patients \end{split}$	Increase of Hb \geq 20 g/L (but Hb < 120 g/L) for non-RBC transfusion-dependent patients; or reduction \geq 50% of transfusion requirement for RBC transfusion-dependent patients	Decrease of Hb ≥ 20 g/L or transfusion requirement for non-RBC transfusion-dependent patients; or increase ≥ 50% of transfusion requirement for RBC transfusion- dependent patients
Splenomegaly*	Spleen not palpable	Decrease of spleen size \geq 50% in patients with spleen size \leq 10 cm from the left costal margin; or decrease of spleen size \geq 30% in patients with spleen size $>$ 10 cm from the left costal margin	Increase of spleen size \geq 50% in patients with spleen size \leq 10 cm from the left costal margin; or increase of spleen size \geq 30% in patients with spleen size $>$ 10 cm from the left costal margin
Constitutional symptoms†	Absence of constitutional symptoms	n/a	Appearance of constitutional symptoms
Platelet (PTL) count	PTL count 150 \times 10 ⁹ /L to 400 \times 10 ⁹ /L	Decrease of PTL count \ge 50% without normalization in patients with PTL count $> 800 \times 10^{9}$ /L; or increase of PTL count \ge 50 \times 10 ⁹ /L without normalization for patients with PTL count $< 100 \times 10^{9}$ /L	n/a
White blood cell (WBC) count	WBC count 4 \times 10 ⁹ /L to 10 \times 10 ⁹ /L	Decrease of WBC count \ge 50% without normalization in patients with WBC count $> 20 \times 10^{9}$ /L; or increase of WBC count $\ge 1 \times 10^{9}$ /L without normalization in patients with WBC count $< 4 \times 10^{9}$ /L	n/a

Values must be stable for at least 4 weeks

n/a indicates not applicable.

*Measured in cm below the left costal margin.

†Unexplained recurrent fever 38.0°C or above, drenching night sweats, or 10% or more body weight loss.

Table 4. Definition of clinicohematologic response

Response type	Definition
Complete response	Complete response in all the criteria
Major response	Provided that the criteria for complete response are not satisfied:
	 Any response in anemia and splenomegaly without progression in constitutional symptoms, OR
	 Complete response in anemia, or partial response in anemia that is transfusion dependent, and response in constitutional symptoms without progression in splenomegaly, OR
	 Any response in splenomegaly and response in constitutional symptoms without progression in anemia
Moderate response	Provided that the criteria for major response are not satisfied:
	 Complete response in anemia with progression in splenomegaly, OR
	Partial response in anemia without progression in splenomegaly, OR
	 Any response in splenomegaly without progression in anemia and constitutional symptoms
Minor response	Provided that the criteria for moderate response are not satisfied:
	Any response in WBC or platelet count without progression in anemia, splenomegaly, or constitutional symptoms
No response	Any response that does not satisfy minor response

Definition of cytogenetic response

The assessment of cytogenetic response was recommended to be dependent on the analysis of 20 metaphases using conventional cytogenetic techniques. A major response was defined as the failure to detect a cytogenetic abnormality in those cases with a preexisting abnormal karyotype, while a minor response was defined as a 50% or greater reduction in abnormal metaphases. Fluorescence in situ hybridization may be used as a supplement to follow a specific defined cytogenetic abnormality.

Discussion

In clinical research, the clinicohematologic, histologic, and cytogenetic responses to new therapeutic agents for MMM are the most important objective, and response rates may provide support for approval by regulatory agencies. In this work, we provide response definitions that are valuable for assessing the clinical outcomes of different therapeutic strategies in MMM, from palliative therapies to therapies altering the natural history of the disease. The assumption of this project is that the assessment of the response to treatments in MMM may be a priori graded according to trial designs and outcomes, from the unique clinicohematologic re-

Table 5. Reference value of bone marrow cellularity in selected age groups

Age, y	Percent hematopoietic area*
20-30	60-70
40-60	40-50
70 or older	30-40

*The cellularity should be measured as percent hematopoietic area, measured by disregarding the first 2 subcortical bone marrow lacunae, if hypocellular.¹⁸

Table 6. Grading of bone marrow fibrosis

Grading	Description*
MF-0	Scattered linear reticulin with no intersections (crossovers)
	corresponding to normal bone marrow
MF-1	Loose network of reticulin with many intersections, especially in
	perivascular areas
MF-2	Diffuse and dense increase in reticulin with extensive
	intersections, occasionally with focal bundles of collagen
	and/or focal osteosclerosis
MF-3	Diffuse and dense increase in reticulin with extensive
	intersections and coarse bundles of collagen, often
	associated with osteosclerosis

*The quality of the reticulin stain should be assessed by detection of normal staining in vessel walls as internal control. The degree of myelofibrosis should be assessed by disregarding lymphoid nodules and vessels and disregarding fibers framing adipocytes. Areas of prominent scleredema and/or scarring should be included in the overall grading of myelofibrosis. Fiber density should be assessed in hematopoietic areas.¹⁸

sponse to an extended definition of response, including histologic and cytogenetic evaluation.

In the absence of a specific biologic marker for the disease, a definition of response in MMM is a complex issue necessitating the incorporation of multiple criteria. The task is further complicated by the paucity of trials and ad hoc studies that have reported the statistical information needed to synthesize the evidence. We used a combination of statistical and consensus methodologies for best definitions of improvement. The core set of candidate clinicohematologic criteria identified by the AB was further modified according to their sensitivity to change and to face and construct validity. The results of the CC suggest that patients with MMM, when evaluated for the clinicohematologic response, should be assessed first according the variations of 3 major criteria: anemia, spleen size, and constitutional symptoms. Variations in platelet count and WBC count were identified as minor criteria that may serve to define a minor response to therapy.

Three other criteria were selected in the early phase of this project as having importance in the assessment of response to treatment. They were quality of life, CD34⁺ cells in peripheral blood,¹⁹ and serum LDH. The first is of importance in therapies that do not impact on disease progression but on patient well-being. The 2 other parameters are biomarkers that serve as response criteria for myeloproliferation. However, the AB deemed their reliability and applicability not to fit with a clinically consistent definition of response, and they were not included in the response definition but were recommended as monitoring parameters during experimental therapies.

Monitoring the changes in bone marrow histology after a period of treatment is not routine in clinical practice and in clinical trials. However, drugs that promise to change the natural course of the disease need to be assessed for their impact on histopathology of the bone marrow. The most frequently used grading systems for bone marrow fibrosis are based on the Bauermeister scale,²⁰ modified by Manoharan et al.²¹ A consensus panel simplified these previous descriptions of scorings of fiber density by reducing them to 4 grades, including the normal reticulin density, to reduce overlapping among the grades and to achieve a higher degree of reproducibility in routine diagnosis. Confusion created in former systems, wherein normal reticulin is classified as "grade 1," was reduced by classifying normal reticulin as "grade 0."

Chromosomal alterations in MMM have a major biologic and prognostic relevance. The therapeutic agents in use today are not able to modify the frequency of chromosomal abnormalities. However, high-dose chemotherapy followed by stem-cell transplantation is a potentially curative therapy, and the cytogenetic analysis is a good marker of disease modification.

We believe that the response criteria presented in this paper are a promising new tool for monitoring disease activity and for assessing therapeutic outcomes in patients with MMM. These criteria will provide a means to compare the results from different patient cohorts and are recommended to facilitate communication within the scientific community.

Acknowledgments

Members of the panel of the Vienna CC on clinicohematologic diagnostic criteria for MMM and the panel of the Palermo CC on histologic diagnostic criteria for MMM are listed in "Appendix."

Appendix

The panel of the Vienna CC on clinicohematologic diagnostic criteria for MMM was composed of Jean Francois Abgrall, Service d'Hematologie Biologique, Hopital La Cavale Blanche, Brest Cedex, France; Giovanni Barosi, Laboratory of Clinical Epidemiology, Istituto di Ricovero e Cura a Carattere Scientifico (IRCCS) Policlinico S. Matteo, Pavia, Italy; Dominique Bordessoule, Service d'Hématologie Clinique, Limoges, France; Jean Briere, Department of Hematology, Hopital Beaujon, Clichy, France; Francisco Cervantes, Hematology Department, Hospital Clinic, L'Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain; Jean-Loup Demory, Département d'Hématologie, Université Catholique de Lille, France; Brigitte Dupriez, Service d'Hématologie Clinique,

References

- 1. Tefferi A. Myelofibrosis with myeloid metaplasia. N Engl J Med. 2000;342:1255-1265.
- Barosi G. Myelofibrosis with myeloid metaplasia. Hematol Oncol Clin North Am. 2003;17:1211-1226.
- Barosi G, Ambrosetti A, Finelli C, et al. The Italian Consensus Conference on diagnostic criteria for myelofibrosis with myeloid metaplasia. Br J Haematol. 1999;104:730-737.
- Thiele J, Imbert M, Pierre R, Vardiman JW, Brunning RD, Flandrin G. Chronic idiopathic myelofibrosis. In: Jaffe ES, Harris NL, Stein H, Vardiman JW, eds. WHO Classification of Tumors: Tumors of Haematopoietic and Lymphoid Tissues. Lyon, France: IARC Press; 2001:35-38.
- Hasselbalch HC, Bjerrum OW, Jensen BA, et al. Imatinib mesylate in idiopathic and postpolycythemic myelofibrosis. Am J Hematol. 2003;74: 238-242.
- Barosi G, Grossi A, Comotti B, Musto P, Gamba G, Marchetti M. Safety and efficacy of thalidomide in patients with myelofibrosis with myeloid metaplasia. Br J Haematol. 2001;114:78-83.
- Mesa RA, Steensma DP, Pardanani A, et al. A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. Blood. 2003;101:2534-2541.

- Marchetti M, Barosi G, Balestri F, et al. Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. J Clin Oncol. 2004;22:424-431.
- Faoro LN, Tefferi A, Mesa RA. Long-term analysis of the palliative benefit of 2-chlorodeoxyadenosine for myelofibrosis with myeloid metaplasia. Eur J Haematol. 2005;74:117-120.
- Cortes J, Albitar M, Thomas D, et al. Efficacy of the farnesyl transferase inhibitor R115777 in chronic myeloid leukemia and other hematologic malignancies. Blood. 2003;101:1692-1697.
- Rondelli D, Barosi G, Bacigalupo A, et al. Allogeneic hematopoietic stem cell transplantation with reduced intensity conditioning in intermediate or high risk patients with myelofibrosis with myeloid metaplasia. Blood. 2005;105:4115-4119.
- White LJ, Ball JR. The clinical efficacy assessment project of the American College of Physicians. Int J Technol Assess Health Care. 1985;1: 169-185.
- Dupriez B, Morel P, Demory JL, et al. Prognostic factors in agnogenic myeloid metaplasia: a report on 195 cases with a new scoring system. Blood. 1996;88:1013-1018.
- Corzillius M, Fortin P, Stuki G. Responsiveness and sensitivity to change of SLE disease activity measures. Lupus. 1999;8:655-659.

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The panel of the Palermo CC on histologic diagnostic criteria for MMM was composed of Silvia Asioli, Institute for Pathology, University of Reggio Emilia, Italy; Stefano Ascani, Institute of Anatomic Pathology, University of Perugia, Terni, Italy; Emanuela Boveri, Institute for Pathology, IRCCS Policlinico S. Matteo and University of Pavia, Italy; Fabio Facchetti, Department of Pathology I, Spedali Civili, Brescia, Italy; Franco Fedeli, Institute for Pathology, University of Pathology, University of Palermo, Italy; Vito Franco, Institute of Pathology, University of Palermo, Italy; Vito Franco, Institute of Pathology, University of Cologne, Germany; Attilio Orazi, Indiana University School of Medicine, Indianapolis; Claudio Tripodo, Institute of Pathology, University of Cologne, Germany; John van der Walt, Department of Histopathology, Saint Thomas Hospital, London, United Kingdom.

- Delbecq AL, van de Ven AH, Gustafson DH. Group Techniques for Program Planning: A Guide to Nominal Group and Delphi Processes. Glenview, IL: Scott, Foresman and Co; 1975.
- Sim J, Wright CC. The kappa statistic in reliability studies: use, interpretation, and sample size requirements. Phys Ther. 2005;85:257-268.
- Cheson BD, Bennett JM, Kantarjian H, et al. World Health Organization (WHO) international working group. Report of an international working group to standardize response criteria for myelodysplastic syndromes. Blood. 2000;96:3671-3674.
- Thiele J, Kvasnicka HM, Facchetti F, Franco V, Van der Walt J, Orazi A. European consensus for grading of bone marrow fibrosis and assessment of cellularity. Haematologica. 2005;98:1128-1132.
- Barosi G, Viarengo G, Pecci A, et al. Diagnostic and clinical relevance of the number of circulating CD34+ cells in myelofibrosis with myeloid metaplasia. Blood. 2001;98:3249-3255.
- Bauermeister DE. Quantitation of bone marrow reticulin—a normal range. Am J Clin Pathol. 1971;56:24-31.
- Manoharan A, Horsley R, Pitney WR. The reticulin content of bone marrow in acute leukaemia in adults. Br J Haematol. 1979;43:185-190.