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The Italian Consensus Conference on Diagnostic Criteria for Myelofibrosis with Myeloid Metaplasia

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Summary. The purpose of this work was to develop a definition of myelofibrosis with myeloid metaplasia (MMM) using diagnostic criteria that would remain valid within the set of patients with chronic myeloproliferative disorders or myelodysplastic syndromes. A list of 12 names for the disease and 37 diagnostic criteria were proposed to a Consensus Panel of 12 Italian experts who ranked them in order so as to identify a core set of criteria. The Panel was then asked to score the diagnosis of 46 patient profiles as appropriate or not appropriate for MMM. Using the experts' consensus as the gold standard, the performance of 90 possible definitions of the disease obtained through the core set was evaluated. 'Myelofibrosis with myeloid metaplasia' ranked as the preferred name of the disease. 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 consisted of: splenomegaly of any grade; anisopoikilocytosis with tear-drop erythrocytes; the presence of circulating immature myeloid cells; the presence of circulating erythroblasts; the presence of clusters of megakaryoblasts and anomalous megakaryocytes in bone marrow sections; myeloid metaplasia. The definition of the disease with the highest final score was as follows: necessary criteria plus any other two criteria when splenomegaly is present or any four when splenomegaly is absent. The use of this definition will help to standardize the conduct and reporting of clinical studies and should help practitioners in clinical practice.

Keywords: myelofibrosis with myeloid metaplasia, consensus conference, diagnostic criteria, chronic myeloproliferative disorders, myelodysplastic syndromes.

The disorder formerly referred to by various names but which we will, as a result of the present work, call myelofibrosis with myeloid metaplasia (MMM), belongs to the clonal proliferations of haemopoiesis categorized among the spectrum of chronic myeloproliferative disorders (CMD). The need to unequivocally distinguish individual clinical entities among CMD led to *ad hoc* committees which developed diagnostic criteria, and the literature now reports parameters designed to identify certain ones such as chronic myeloid leukaemia (CML) (Bennett *et al*, 1994), polycythaemia vera (PV) (Berlin, 1975) and essential thrombocythaemia (ET) (Murphy *et al*, 1986). Criteria for the diagnosis of MMM were first proposed by Laszlo (1975) of the Polycythemia Vera Study Group (PVSG). The features agreed upon included fibrosis involving more than one-third the sectional area of a bone marrow biopsy, splenomegaly, leucoerythroblastic blood reaction, the absence of an increased red blood cell mass and the absence of the Philadelphia chromosome. However, over the last 20 years a wide range of clinical and pathologic phenotypes of the disease (Bentley *et al*, 1977; Barosi *et al*, 1983, 1991; Polino *et al*, 1986) and mixed or transitional CMD with features resembling MMM (Krauss, 1966; Pettit *et al*, 1976) have been reported. Moreover, among the disorders categorized under the heading of myelodysplastic syndromes (MDS) (Bennett *et al*, 1982; Kouides & Bennet, 1996), the possibility of true myeloproliferative characteristics as in chronic myelomonocytic leukaemia (CMMoL) (Fenaux *et al*,

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1987; Storniolo *et al*, 1990; Bennett *et al*, 1994; Greenberg *et al*, 1997; Niemeyer *et al*, 1997), presentation with bone marrow fibrosis (Pagliuca *et al*, 1989; Verhoef *et al*, 1991; Maschek *et al*, 1992; Krishnan & Seldon, 1996) and mixed myelodysplastic and myeloproliferative features (Neuwirtova *et al*, 1996) make the distinction between MMM difficult in some cases. These reasons led most of the published MMM series to report patient populations which were less strictly defined than that required by the originally proposed criteria. In particular, the parameters of normal or decreased red cell mass (Barosi *et al*, 1988; Visani *et al*, 1990; Dupriez *et al*, 1996), and the presence of splenomegaly at diagnosis of the disease (Cheng, 1979; Rupoli *et al*, 1994; Barosi *et al*, 1998), do not always seem to have been met in all patients. Moreover, others did not consider bone marrow fibrosis to be a necessary diagnostic criterion in early hypercellular stages when haemopoiesis is characterized by an abnormal cytologic appearance of megakaryocytes (Georgii *et al*, 1990; Thiele *et al*, 1996) and the term 'chronic megakaryocytic-granulocytic myelosis' was coined to describe the early nonfibrotic stage of myelofibrosis (Georgii *et al*, 1990).

The lack of accepted standardization of criteria for distinguishing among the spectrum of similar forms may lead to nonhomogenous inclusion of patients in clinical trials with the risk of reporting bias, ambiguous interpretation of results, and the inability to compare therapies. Perceiving the need for rigorous, consistent and feasible criteria for the diagnosis of MMM, we undertook this project. Our purpose was to identify a core set of criteria and to develop a definition of MMM that would aid in the classification of individual patients as well as be applicable to future clinical studies. We envisioned that the definition of MMM might also be useful for physicians assessing patients in routine practice.

METHODS

The Italian Consensus Conference (CC) on Diagnostic Criteria for MMM Project was developed by a multistep process, based on the NIH approach (White & Ball, 1985) with some modifications. This process is described below and summarized in Fig 1.

An 18-member Advisory Council was formed in June 1995. It was composed of haematologists with experience and interest in MMM, members of the Italian Cooperative Group on MMM of the GIMMC (Italian Group on Chronic Myeloproliferative Diseases), constituted under the auspices of the Italian Society of Haematology. The objectives of the Advisory Council were: (1) to define the aims of the project and to frame the operative and clinical context (needs-assessment phase); (2) to review the literature for diagnostic criteria (the literature review phase); (3) to select the members of the CC Panel and to organize the consensus development process aimed at defining the disease (the consensus phase).

The needs-assessment phase. After three successive meetings and much free discussion, the Advisory Council under the leadership of the Prime Organizer (G.B.) agreed on the aim of the project: 'to choose the best name for and to develop a diagnostic definition of the disorder that would remain valid in a set of patients with CMD or MDS'. The Council decided to use the following terminology throughout the project. A 'criterion' refers to a 'single biological or clinical characteristic, such as a test result, clinical investigation result, or histologic characteristic that is assessable and binary (present/absent)'. A 'positive' criterion was defined as a criterion the presence of which indicated MMM and a 'negative' criterion as one the presence of which excluded MMM. 'Necessary criterion' was defined a criterion that must be present and the presence of which must be ascertained in order for patients to be defined as having MMM.

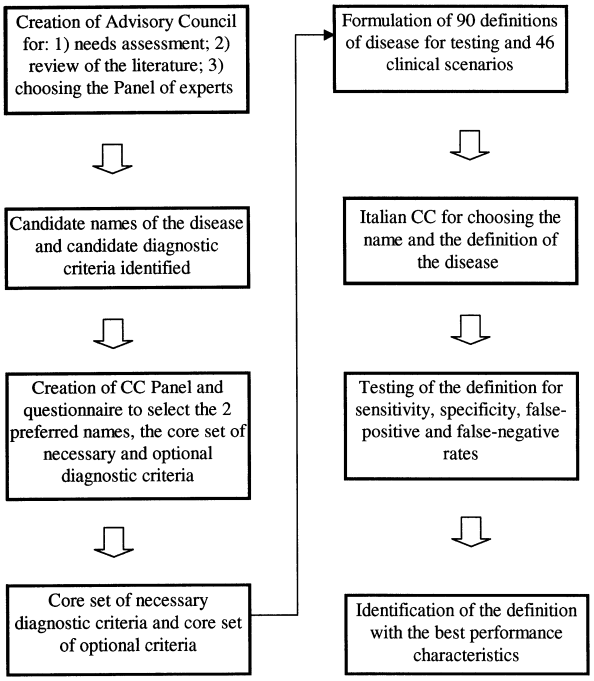

Fig 1. Process of choosing the preferred name, the core set of diagnostic criteria and, using the core set, a definition of MMM.

The literature review phase. The aims set by the Advisory Council in reviewing the literature were the following: (1) to enumerate the criteria used for diagnosing MMM in the literature (historic criteria); (2) to identify other features of MMM that could be proposed as diagnostic criteria (newly proposed criteria); (3) to calculate the sensitivity and specificity of both historic and newly proposed criteria (candidate criteria) for MMM among other CMD and MDS.

The Advisory Council searched the MEDLINE database for relevant articles according to a strategy that included 10 pertinent keywords. Studies published between 1960 and 1996 inclusive were screened and the bibliographies of retrieved articles and conference proceedings were examined manually.

For the 'historic criteria' search phase, all studies retrieved were included and the investigators from the Advisory Council independently gathered the criteria used for the diagnosis of MMM. Most of the time these were taken from the Materials and Methods section of the papers, but when reviews or commentaries were examined the criteria were drawn from every part of the paper.

For the 'newly proposed criteria' search phase, only original papers were retrieved and the members of the Council were independently assigned to peruse literature dealing with one of the following topics: clinics, pathology, cytogenetics, immunology, imaging and isotopic studies and *in vitro* cultures. The reviewers were to search for new candidate criteria for the diagnosis of MMM.

For the calculation of the specificity and sensitivity phase, only studies dealing with Philadelphia-negative CMD or MDS with bone marrow fibrosis (the diagnostic context) in which more than 10 subjects were enrolled and in which data necessary to calculate both the sensitivity and specificity were reported were included. The Advisory Council assumed that the diagnostic characteristic of any criterion drawn from the literature represented an index of diagnostic confidence which the scientific community had given to that criterion. The performance of any criterion was characterized by its sensitivity and specificity and by its diagnostic efficiency (true positive plus true negative rates), i.e. the probability that a criterion correctly identified MMM patients within the diagnostic context. Diagnostic efficiency was obtained after correction for disease prevalence, derived from the incidence and mean duration as reported in the literature (Bilgrami & Greenberg, 1995; Tefferi *et al*, 1995a, b; Maynadie *et al*, 1996). The Advisory Council assumed that the disutility or cost of false-positive criteria and the disutility of false-negative criteria were equal.

The consensus phase. Twelve Italian scientists were asked to join the Panel for the CC Project. 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 haematology and medical oncology, and both academic and hospital representatives were included; they were chosen for their representativeness and prominent position in Italian medical societies.

A pre-consensus conference questionnaire was mailed to each Panel member asking them: (1) to rank the top choice among the disease designations used by the medical literature; (2) to select the necessary criteria, that is the criteria from the list of candidate criteria which should necessarily be ascertained and be present to diagnose MMM; (3) to rank the top six choices among candidate criteria, excluding the necessary ones (optional criteria). An 'other' category was provided to add names and criteria not included in the list. The panelists were also provided with a booklet that summarized the aims of the Project and the results of the literature search phase. For all candidate criteria the statistical performance, when available, was included. All the questionnaires were returned and the names of the disease, the necessary criteria and the candidate criteria were ranked according to their priority votes. The two necessary and the six optional criteria which ranked highest formed the core set of criteria.

A CC was held in Bologna, Italy, in May 1997. The meeting was attended by the 12 members of the CC Panel with the assistance of two members of the Advisory Council (G.B. and N.L.L.). The overall aim of the meeting was to decide upon the final name of the disease and a definition of the disease based on a core set of criteria, using a combination of statistical and consensus formation techniques (Delbecq *et al*, 1975). In order to achieve this there were three objectives, which are described in consecutive order below.

1. *Rate the two names of the disease receiving the highest scores from the questionnaire using the nominal group technique*. Participants were asked to silently choose the preferred name. If an 80% consensus on the preferred name was not achieved, the choices were discussed in round-robin fashion and a second vote taken. If an 80% consensus was still not attained, the name was declared undecidable and no further attempt was made.

2. *Rate each of 46 paper patient profiles as appropriate or not appropriate for a diagnosis of MMM using the nominal group technique*. Existing data bases were exploited to build 46 patient profiles to be presented to conference attendees. The GIMMC had conducted a retrospective trial to evaluate the incidence of blast transformation in MMM ($n = 560$) (Barosi *et al*, 1998) and the Institute of Internal Medicine and Medical Oncology of the University Hospital of Pavia had conducted a retrospective trial to evaluate prognostic factors for MDS ($n = 148$) (Ascari *et al*, 1997). These data bases were selected as a source of patients. The profiles selected were those of patients with doubts regarding the diagnostic classification raised by their clinical records. Absolute values at diagnosis were shown for each criterion. Participants at the CC were asked to silently rate each of the 46 patient profiles as MMM or not. The moderator then asked each member how he had voted on each profile. If an 80% consensus about whether a patient had MMM was not achieved, the case 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 in the nominal group.

3. *Using the physicians' consensus judgement as the gold standard, calculate the percent false-positive and false-negative rates, chi-square, sensitivity and specificity for each of the 90 definitions of MMM*. By using combinations of the variables in the core set selected on the questionnaire, the Advisory Council developed for testing a set of 90 sound definitions of MMM. Then the ability of the 90 candidate definitions of the disease to classify individual patients as having MMM or not was evaluated, and the agreement between the decision based on the criteria and the consensus of the physicians was assessed. Only patient profiles for which physician consensus was achieved were used. For each definition, we calculated the chi-square (1 degree of freedom) and the corresponding P value, sensitivity (ability of the definition to identify as having MMM a patient who had been classified as having MMM by the physicians), specificity (ability of the definition to identify as not having MMM a patient who had been classified as not having MMM by the physicians), rate of false-positivity ([number falsely identified as having MMM by criteria/all patients identified as having MMM] $\times$ 100), and rate of false-negativity ([number falsely identified as not having MMM by the criteria/all patients identified as not having MMM] $\times$ 100). Two-sided 95% confidence intervals (one-sided 97·5% for values of 100%) for both sensitivity and

specificity were calculated by the exact binomial method. Those definitions of the disease showing either a sensitivity or specificity of <80% were eliminated from further consideration. We used the kappa statistic as an additional measure of agreement between the physicians' evaluation and the definitions: k values $\geqslant 0{\cdot}7$ were considered to be evidence of agreement.

RESULTS

Preferred name of the disease

Among the 12 names for the disease found in the literature, the questionnaires returned showed a preference for: 'myelofibrosis with myeloid metaplasia' and 'idiopathic myelofibrosis'. Using the consensus formation technique, the CC Panel agreed upon the designation 'myelofibrosis with myeloid metaplasia'.

Candidate criteria to be evaluated

The Advisory Council listed 21 historic criteria (16 positive and five negative), along with six new positive and 10 new negative criteria used for the diagnosis of other CMD or MDS, to be included as candidate criteria for the diagnosis of MMM. Of this set of 37 criteria, 21 possessed data from the literature for characterizing their diagnostic performance within the group of Philadelphia-negative CMD and 14 for assessing performance within the MDS with bone marrow fibrosis. Table I reports the sensitivity and specificity of these criteria and their diagnostic efficiency. These data were presented to the CC Panel in the booklet for their personal evaluation.

The four criteria with the highest preference rate from the questionnaire as necessary for diagnosis were: (1) bone marrow fibrosis of any grade; (2) bone marrow fibrosis greater than a third of the biopsy area; (3) absence of the Philadelphia chromosome in peripheral blood cells; (4) lack of BCR-ABL rearrangement in peripheral blood cells. When the other criteria were ranked according to their priority score, the six criteria for the core set included the following: (1) splenomegaly of any grade; (2) anisopoikilocytosis with tear-drop 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.

Necessary criteria

Using the nominal group technique a consensus was sought on the necessary criteria chosen by the questionnaire. A consensus was reached on either presence of the Philadelphia chromosome or BCR-ABL rearrangement in peripheral blood cells. No consensus on which of the two mutually exclusive criteria for defining the necessary degree of bone marrow fibrosis was reached, and the CC Panel suggested changing the definition of the criterion. After the CC, the Advisory Council considered the issues raised during the CC

Table I. Diagnostic performance of the criteria for MMM with respect to other Philadelphia-chromosome-negative chronic myeloproliferative disorders (polycythaemia vera, PV, and essential thrombocythaemia, ET) and myelodysplastic syndromes with bone marrow fibrosis (MDS with fibrosis). When no data on MDS with bone marrow fibrosis were present in the literature, the diagnostic efficiency was that of PV plus ET alone.

Criteria	Sensitivity	Specificity		Diagnostic efficiency
		PV + ET	MDS with fibrosis	
Anisopoikilocytosis with tear-drop erythrocytes	0·90	0·90	0·47	0·89
Anaemia	0·72	0·91	0·05	0·88
Erythroblasts in peripheral blood	0·69	0·95	0·58	0·83
Immature myeloid cells in peripheral blood	0·87	0·85	0·58	0·82
Dry-tap	0·66	0·90	0·15	0·81
Myeloid metaplasia	0·84	0·69	0·69	0·73
Bone marrow fibrosis greater than one third of biopsy area	0·99	0·63	0	0·73
Increase in serum procollagen III peptide	0·75	0·75	–	0·73
Marrow hypocellularity	0·29	0·93	0·77	0·73
Hepatomegaly	0·72	0·67	0·73	0·67
Splenomegaly of any grade	0·92	0·55	0·65	0·61
Spontaneous growth of BFU-E	0·49	0·89	–	0·26
Normal or reduced red cell volume	0·68	0·55	0	0·53
Lymphoadenomegaly	0·11	0·54	0	0·65
Presence of clusters of megakaryoblasts and atypical megakaryocytes	0·60	0·33	–	0·37
Spontaneous growth of CFU-Meg	0·71	0·25	–	0·45
Decrease of marrow fat	0·84	0·12	–	0·31
LAP score normal or increased	0·88	0·08	–	0·31
Absence of Philadelphia chromosome in peripheral blood cells	1	0	0	0·31
Marrow hypercellularity	0·22	0·21	0·35	0·11

Table II. Final results for the eight best definitions of MMM.

Definition (criteria other than necessary ones, i.e. bone marrow fibrosis and lack of the genetic marker of CML)	Chi-square*	Sensitivity and 95% confidence intervals	Specificity and 95% confidence intervals	False-positive rate	False-negative rate	*K* statistics
Any two of the others present when splenomegaly is present; any four of the others present when splenomegaly is absent	21·1	0·88 (0·69–0·97)	1 (0·63–1)†	0	0·27	0·83
Any two of the others present when splenomegaly or anisopoikilocytosis with tear-drop erythrocytes is present; any four of the others present when splenomegaly and anisopoikilocytosis with tear-drop erythrocytes are absent	14·8	0·92 (0·74–0·99)	0·75 (0·35–0·97)	0·08	0·25	0·67
Any two of the others present when splenomegaly is present	14·3	0·76 (0·55–0·91)	1 (0·63–1)†	0	0·43	0·66
Any two of the others present when splenomegaly and anisopoikilocytosis with tear-drop erythrocytes are present; the four others present when splenomegaly and anisopoikilocytosis with tear-drop erythrocytes are absent	12·7	0·72 0·51–0·88)	1 (0·63–1)†	0	0·47	0·62
Any two of the others present when splenomegaly is present; the other five present when splenomegaly is absent	12·7	0·72 (0·51–0·88)	1 (0·63–1)†	0	0·47	0·62
Any two of the others present when splenomegaly or anisopoikilocytosis with tear-drop erythrocytes is present	12·7	0·72 (0·51–0·88)	1 (0·63–1)†	0	0·47	0·62
Any other one present when splenomegaly is present; any three of the others present when splenomegaly is absent	10·3	1 (0·86–1)†	0·38 (0·08–0·75)	0·17	0	0·56

* *P* values <0·001. † One-sided 97·5% confidence intervals.

discussion, reconvened and framed the following alternative definition of bone marrow fibrosis: 'microscopic evidence of reticulin fibres at 100× in any area of bone marrow sections in biopsies no smaller than 3×15 mm'. The question was mailed and 80% of the replies agreed with this definition of the bone marrow fibrosis necessary for diagnosis.

Identification of the best performing definition

The 12 Panel members scored 25 of the 46 patient profiles as having MMM, eight as not having MMM, and 13 as uninterpretable. Eight of the 90 definitions of MMM showed chi-square >10. These eight definitions, their corresponding chi-square values, sensitivity and specificity, confidence intervals, *P* values, false-positive and false-negative rates are shown in Table II. The definition of MMM that scored highest was as follows (Table III): diffuse bone marrow fibrosis necessarily present and Philadelphia chromosome or BCR-ABL rearrangement in peripheral blood cells necessarily absent; any two of the other core set criteria present when splenomegaly is present; any four of the other core set criteria present when splenomegaly is absent.

Table III. The Italian criteria for the diagnosis of myelofibrosis with myeloid metaplasia.

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 tear-drop erythrocytes
3. Presence of circulating immature myeloid cells
4. Presence of circulating erythroblasts
5. Presence of cluster 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; the two necessary criteria plus any other four optional criteria when splenomegaly is absent.

DISCUSSION

In this work we report a consensus on the diagnostic definition of myelofibrosis with myeloid metaplasia. In the absence of a specific biological marker for the disease, we were aware that searching for a definition of MMM raised both a true diagnostic issue, i.e. which diagnostic criteria and how to use them for the diagnosis, and a classificatory one, i.e. how to distinguish this disease among a spectrum of disorders of the same nature and with similar features. To focus the problem, the Advisory Council clearly stated that the aim of this project was to arrive at a definition of MMM within the limited scenario of CMD or MDS.

The task of finding a consensus for diagnostic criteria was complicated by the fact that the area is usually characterized by few *ad hoc* studies reporting the statistical information needed for summing up the evidence. Actually, of the 37 candidate criteria retrieved from the literature, only 21 had studies that were useful for evaluating how specific and sensitive they were in classifying MMM among other chronic Philadelphia-negative CMD, and only 14 showed such studies for a similar evaluation among MDS with bone marrow fibrosis, i.e. our diagnostic context. The Panel put the highest value on criteria sensitivity when it had to choose the criteria that must be present for diagnosis, i.e. absence of the genetic marker of CML and evidence of bone marrow fibrosis, and put value on the overall measure of diagnostic efficiency, i.e. a summary index of positive and negative predictive value, when it had to identify the optional criteria.

Using consensus formation and a statistical approach, the results of this project suggest that MMM can be defined as follows (Table III): bone marrow fibrosis and lack of the genetic marker of CML necessarily present; any two of the six optional criteria of the core set present if splenomegaly is present, or any four of the optional core set criteria present if splenomegaly is absent. As most of the formulations of the criteria were drawn from the literature, one could note ambiguity in these formulations. For example, pathologists might feel uncertain about how to define exactly 'clusters of megakaryoblasts and anomalous megakaryocytes in the bone marrow sections' (Rupoli *et al*, 1994; Thiele *et al*, 1996). 'Myeloid metaplasia' is also a criterion for which the biological meaning is clear but for which the methods of detection vary. However, investigators in future trials on the disease should feel free to replace this definition of the criterion with other more specific definitions or to better specify which method of assessment should be fulfilled for the inclusion of patients. The only source of disagreement about a criterion definition among the consensus panelists was on bone marrow fibrosis. As a result, the new formulation presented by the Advisory Committee and accepted by the panelists is as follows: 'microscopic evidence of reticulin fibres at 100× in any area of bone marrow sections in biopsies no smaller than 3×15 mm'.

The definition of MMM formulated in this work is one that was constructed with features of the disease that are not universally agreed upon for enrolling cases in clinical trials or used by clinicians to diagnose the disease in individual patients. The panelists agreed on the necessary presence of bone marrow fibrosis for defining MMM. As a consequence, in CMD without myelofibrosis but with megakaryocyte maturation defects and atypical histotopography, classified by some pathologists as stage 0 myelofibrosis (Georgii *et al*, 1990; Thiele *et al*, 1996), a diagnosis of MMM should avoided. The unnecessary red blood cell volume measurement means that both transitional disorders with increased red cell volume and bone marrow fibrosis (Pettit *et al*, 1976), as well as post-polycythaemia myeloid metaplasia with persistently increased red cell volume (Ellis *et al*, 1986), should be not strictly excluded. It is thus the intention of the panelists that the term MMM encompass patients with both idiopathic disease and one that transforms from other CMD.

The results of this work derived from a structured consensus process and a statistical analysis on the experts' reactions to 42 real cases. The performing characteristics of

the resulting disease definition, i.e. its specificity and sensitivity, should be interpreted as a result of uncertainty inherent both to the consensus process and to the panelists' idea of the disease. The former depends on the numbers chosen for the sample of experts and cases used during the consensus process; the latter captures the absence of clear markers for defining the disease. The resulting definition had 100% specificity and 88% sensitivity, which thus assured no false positives, but some false negatives. These criteria therefore seemed to be appropriate when used for enrolling patients in clinical trials.

A consequence of the results of this Project is that patients to be included in studies on MMM will have to be analysed for the absence of the CML genetic marker, even in cases in which a diagnosis of MMM seems clear. Performing a chromosomal or molecular study in MMM patients is not the rule today (Kvasnicka *et al*, 1997; Visani *et al*, 1990; Dupriez *et al*, 1996). Another important consequence of the results is that a pivotal role in the diagnosis is in the hands of pathologists. They have to make a judgment on bone marrow fibrosis and on the presence of pathological clusters of megakaryoblasts or anomalous megakaryocytes.

In conclusion, this Project proposes a definition of MMM that has >80% sensitivity and specificity. Use of the criteria forming the definition should be required for communication within the scientific community and for the inclusion of patients in any scientific trials.

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