CLINICAL TRIALS AND OBSERVATIONS

Revised response criteria for myelofibrosis: International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN) consensus report

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Key Points

- Treatment response criteria for MF must capture drug benefit in terms of symptom burden.
- The current document includes stricter definitions of red cell transfusion need and independence.

The current document is a revision of the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) criteria for treatment response in myelofibrosis (MF) and represents a collaborative effort by the IWG-MRT and the European LeukemiaNet to objectively assess the value of new drugs in inducing morphologic remission or improvement in MF-associated symptomatic burden (MF-SB). Some of the changes in the current revision include stricter definitions of red cell transfusion dependency and independency and consideration of the Myeloproliferative Neoplasm Symptom Assessment Form as a tool to quantify meaningful changes in disease-related symptoms. Six response categories are listed: complete remission (CR) and partial remission signify treatment effects that are consistent with disease modification, whereas drug-induced improvements in MF-SB were annotated as clinical improvement, anemia response, spleen response, or symptoms response. Additional criteria are provided for progressive disease, stable disease, and relapse. The document also includes recommendations for assessing cytogenetic and molecular remissions, without mandating their inclusion for CR assignment. (*Blood*. 2013;122(8):1395-1398)

Introduction

Myelofibrosis (MF) is a pathological entity associated with primary MF, postpolycythemia vera MF, and postessential thrombocythemia MF.[1] These diseases are characterized by clonal myeloproliferation, ineffective erythropoiesis, bone marrow stromal changes, hepatosplenic extramedullary hematopoiesis, and aberrant cytokine expression.[2] At presentation, the disease characteristics of primary MF include palpable splenomegaly in 89%, constitutional symptoms in 27%, moderate-to-severe anemia (hemoglobin < 10 g/dL) in 35%, thrombocytopenia (platelets $< 100 \times 10[9]$/L) in 17%, or marked leukocytosis (leukocytes $> 25 \times 10[9]$/L) in 10%.[3] Patients with MF have shortened survival[4] and greatly compromised quality of life (QoL).[5] Contributing factors for shortened survival include leukemic transformation[5] and thrombohemorrhagic complications[6] and for the compromised quality of life severe anemia (often requiring red cell transfusions), symptomatic enlargement of the spleen and liver, substantial MF-associated symptoms burden (MF-SB), and cachexia.[5] Allogeneic stem cell transplant, using conventional[7] or reduced intensity[8] conditioning, is currently the only treatment modality in MF with the ability to induce long-term disease-free remission. The value of other treatment options, including drug therapy, splenectomy, and radiotherapy, is mostly palliative with uncertain survival benefit.[9] A plethora of new drugs, including thalidomide analogs[10] and Janus kinase[11-13] or mammalian target of rapamycin[14] inhibitors, have been recently developed and evaluated in MF clinical trials. So far, none of these new drugs have displayed selective anti-clonal effect, despite an otherwise remarkable activity in alleviating anemia, splenic discomfort, and constitutional symptoms. In other words, the value of such drugs would be undermined if formal response criteria in MF did not include response categories that capture drug benefit in terms of MF-SB, which impacts health-related QoL. However, there is no good evidence to indicate that responses in anemia, splenomegaly, or symptoms could be used as surrogates for improved survival. Consensus-based definitions of response, in this regard, are designed for the purpose of standardizing response criteria for use in clinical trials and not for use in routine care of patients.

Submitted March 4, 2013; accepted June 27, 2013. Prepublished online as *Blood* First Edition paper, July 9, 2013; DOI 10.1182/blood-2013-03-488098.

The online version of this article contains a data supplement.

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Study design

The current work is the result of a collaborative project by the International Working Group-Myeloproliferative Neoplasms Research and Treatment (IWG-MRT) and European LeukemiaNet (ELN). The document was developed through extensive discussions that took place during the IWG-MRT annual meetings of 2011 and 2012 in Florence, Italy, as well as the ELN MPN subcommittee conferences at the 2011 and 2012 American Society of Hematology annual meetings in San Diego, CA, and Atlanta, GA, respectively. These meetings were led by an expert panel that included authors of the 2006 IWG-MRT response criteria for MF,[15] as well as myeloproliferative neoplasm subcommittee members for ELN. Post- and pre-meeting input from study participants were sought through electronic communications and adjudicated through consensus (see the supplemental Data Set link at the top of the online article for details of the decision process).[16]

The basic principles behind the current revision were to include response categories that suggest disease modification, as well as those that provide objective quantification of drug activity in improving anemia, splenomegaly, and symptoms. In this regard, the expert panel acknowledged the need for strict definitions of red cell transfusion dependency and independency, confirmation of spleen response by imaging studies, and the Myeloproliferative Neoplasm Symptom Assessment Form (MPN-SAF) tool to measure meaningful changes in MF symptoms.[17] The revised criteria also provide recommendations for assessing cytogenetic and molecular responses.

Results and discussion

Table 1 outlines 9 separate categories for the revised IWG-MRT and ELN response criteria for treatment in MF. Table 1 also includes recommendations for cytogenetic and molecular responses, but these responses are not required for assignment as complete (CR) or partial remission (PR). Definitions of red cell transfusion dependency and independency and other items are added as footnotes to Table 1.

The definitions of CR and partial (PR) remissions are somewhat akin to those employed in acute myeloid leukemia[18] and myelodysplastic syndromes,[19] and are meant to highlight drug effects that suggest disease modification or substantial anti-clonal activity. Bone marrow morphologic remission is a requisite for CR and its definition in the current document was intentionally toned down to minimize subjective differences in assessing megakaryocyte morphology. Morphologic remission in the peripheral blood, but not necessarily in the bone marrow, is required for PR assignment. Patients meeting criteria for CR, but who have inadequate blood count recovery are also included in the PR response category to capture disease-modifying activity confounded by drug-related cytopenia.[18] In other words, some drugs might induce prolonged myelosuppressive effect that prevents normal recovery of blood counts despite morphologically normal-appearing marrow.

The IWG-MRT and ELN response categories other than CR and PR were developed in recognition of the profound impact of MF-SB to health-related QoL. The primary contributors of decreased health-related QoL in MF are anemia, marked splenomegaly, and constitutional symptoms. Accordingly, the current revised document includes response definitions for each one of these specific disease features and an additional composite response category, labeled as clinical improvement (CI), and defined as a response in anemia, splenomegaly, or MF-SB that is not associated with progressive splenomegaly (Table 1) or increase in severity of anemia, thrombocytopenia, or neutropenia (Table 1 footnotes). Accordingly, an anemia response that might be associated with progressive splenomegaly (as has been seen with pomalidomide therapy)[20] or spleen response associated with drug-induced anemia (as has been seen with some Janus kinase inhibitors),[11,21] would still be included in an individual response category, although not counted as CI. Similarly, for a symptom response to count as CI, it requires the absence of progressive splenomegaly and treatment-associated anemia.

Recent experience with clinical trials in MF has highlighted the need to establish strict definitions for red cell transfusion dependency and treatment-induced transfusion independency[22]; these are now outlined as footnotes in Table 1. We fully recognize the fact that our consensus-based definitions in this regard are imprecise and do not adequately address the confounding effects of age and race on blood volume and cultural differences in indications for blood transfusion. Some patients with transfusion needs may not meet the strict criteria for transfusion dependency at the time of study enrollment; the expert panel recommends the use of the pre-transfusion hemoglobin level as baseline in such cases. Another confounding element in phase 1 and 2 studies is the possibility that improvement in anemia might be the result of discontinuation of myelosuppressive therapy (eg, hydroxyurea), in preparation for enrollment into clinical trials. This is why phase 3 studies are important in validating observations from phase 2 studies, especially in terms of anemia response. In other words, anemia response in a phase 2 study, without placebo control, should be viewed with caution, but standardizing the criteria should help compare results between phase 2 studies.

The IWG-MRT and ELN expert panel also recognized the highly subjective nature of spleen and liver size assessment by physical examination, and recommended objective confirmation by magnetic resonance imaging (MRI) or computed tomography. The spleen volume reduction thresholds for response in this regard were set at 35% based on recent studies that compared physical examination and MRI assessment of spleen size in patients with MF.[21] In some cases, imaging studies might reveal significant volume reduction that is not captured by physical examination; in such cases, a $\geqslant$ 35% reduction in spleen or liver volume overrides the measurements by physical examination for the purposes of response assignment.

Response in MF-SB is assessed by The MPN-SAF total symptom score (TSS)[17]; the TSS is assessed by the patients themselves and includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Each of the 10 symptoms is scored from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be). The MPN-SAF TSS is a summation of all the individual scores (0-100 scale). A response in MF-SB requires a $\geqslant$50% reduction in the MPN-SAF TSS. An assessment of health-related QoL may also be done in the context of a clinical trial, but given its multifactorial nature, the expert panel agreed that assessing therapy response should focus on MF-SB.

Laboratory investigations on the biology and genetics of MF are likely to identify new drug targets and clarify their pathogenetic contribution of Janus kinase–signal transducer and activator of transcription. This is important considering the failure of currently available drugs in securing selective suppression of clonal myeloproliferation. The availability of more effective and selective antineoplastic drugs in MF will mandate the formal incorporation of cytogenetic and molecular information in future revisions of the current response criteria. In the meantime, strictly defined measurements of palliative value are necessary to justify the therapeutic use of new drugs and allow comparison of their efficacy. In the end, we would like to emphasize the fact that consensus statements do not necessarily provide either accurate or validated surrogates of clinical

Table 1. Revised IWG-MRT and ELN response criteria for MF

Response categories	Required criteria (for all response categories, benefit must last for ≥12 wk to qualify as a response)
CR	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF† and
	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥ 1 × 10^9/L and <UNL;
	Platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
PR	Peripheral blood: Hemoglobin ≥100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH or
	Bone marrow:* Age-adjusted normocellularity; <5% blasts; ≤grade 1 MF†, and peripheral blood: Hemoglobin ≥85 but <100 g/L and <UNL; neutrophil count ≥1 × 10^9/L and <UNL; platelet count ≥50, but <100 × 10^9/L and <UNL; <2% immature myeloid cells‡ and
	Clinical: Resolution of disease symptoms; spleen and liver not palpable; no evidence of EMH
Clinical improvement (CI)	The achievement of anemia, spleen or symptoms response without progressive disease or increase in severity of anemia, thrombocytopenia, or neutropenia§
Anemia response	Transfusion-independent patients: a ≥20 g/L increase in hemoglobin level‖
	Transfusion-dependent patients: becoming transfusion-independent¶
Spleen response#	A baseline splenomegaly that is palpable at 5-10 cm, below the LCM, becomes not palpable** or
	A baseline splenomegaly that is palpable at >10 cm, below the LCM, decreases by ≥50%**
	A baseline splenomegaly that is palpable at <5 cm, below the LCM, is not eligible for spleen response
	A spleen response requires confirmation by MRI or computed tomography showing ≥35% spleen volume reduction
Symptoms response	A ≥50% reduction in the MPN-SAF TSS††
Progressive disease‡‡	Appearance of a new splenomegaly that is palpable at least 5 cm below the LCM or
	A ≥100% increase in palpable distance, below LCM, for baseline splenomegaly of 5-10 cm or
	A 50% increase in palpable distance, below LCM, for baseline splenomegaly of >10 cm or
	Leukemic transformation confirmed by a bone marrow blast count of ≥20% or
	A peripheral blood blast content of ≥20% associated with an absolute blast count of ≥1 × 10(9)/L that lasts for at least 2 weeks
Stable disease	Belonging to none of the above listed response categories
Relapse	No longer meeting criteria for at least CI after achieving CR, PR, or CI, or
	Loss of anemia response persisting for at least 1 month or
	Loss of spleen response persisting for at least 1 month
	Recommendations for assessing treatment-induced cytogenetic and molecular changes
Cytogenetic remission	At least 10 metaphases must be analyzed for cytogenetic response evaluation and
	requires confirmation by repeat testing within 6 months window
	CR: eradication of a preexisting abnormality
	PR: ≥50% reduction in abnormal metaphases
	(partial response applies only to patients with at least ten abnormal metaphases at baseline)
Molecular remission	Molecular response evaluation must be analyzed in peripheral blood granulocytes and
	requires confirmation by repeat testing within 6 months window
	CR: Eradication of a pre-existing abnormality
	PR: ≥50% decrease in allele burden
	(partial response applies only to patients with at least 20% mutant allele burden at baseline)
Cytogenetic/molecular relapse	Re-emergence of a pre-existing cytogenetic or molecular abnormality that is confirmed by repeat testing

EMH, extramedullary hematopoiesis (no evidence of EMH implies the absence of pathology- or imaging study-proven nonhepatosplenic EMH); LCM, left costal margin; UNL, upper normal limit.

*Baseline and posttreatment bone marrow slides are to be interpreted at one sitting by a central review process. Cytogenetic and molecular responses are not required for CR assignment.

†Grading of MF is according to the European classification

Thiele et al. European consensus on grading bone marrow fibrosis and assessment of cellularity. *Haematologica.* 2005;90:1128.

It is underscored that the consensus definition of a CR bone marrow is to be used only in those patients in which all other criteria are met, including resolution of leukoerythroblastosis. It should also be noted that it was a particularly difficult task for the working group to reach a consensus regarding what represents a complete histologic remission.

‡Immature myeloid cells constitute blasts + promyelocytes + myelocytes + metamyelocytes + nucleated red blood cells. In splenectomized patients, <5% immature myeloid cells is allowed.

§See above for definitions of anemia response, spleen response, and progressive disease. Increase in severity of anemia constitutes the occurrence of new transfusion dependency or a ≥20 g/L decrease in hemoglobin level from pretreatment baseline that lasts for at least 12 weeks. Increase in severity of thrombocytopenia or neutropenia is defined as a 2-grade decline, from pretreatment baseline, in platelet count or absolute neutrophil count, according to the Common Terminology Criteria for Adverse Events (CTCAE) version 4.0. In addition, assignment to CI requires a minimum platelet count of ≥25 000 × 10(9)/L and absolute neutrophil count of ≥0.5 × 10(9)/L.

‖Applicable only to patients with baseline hemoglobin of <100 g/L. In patients not meeting the strict criteria for transfusion dependency at the time of study enrollment (see as follows), but have received transfusions within the previous month, the pretransfusion hemoglobin level should be used as the baseline.

¶Transfusion dependency before study enrollment is defined as transfusions of at least 6 units of packed red blood cells (PRBC), in the 12 weeks prior to study enrollment, for a hemoglobin level of <85 g/L, in the absence of bleeding or treatment-induced anemia. In addition, the most recent transfusion episode must have occurred in the 28 days prior to study enrollment. Response in transfusion-dependent patients requires absence of any PRBC transfusions during any consecutive "rolling" 12-week interval during the treatment phase, capped by a hemoglobin level of ≥85 g/L.

#In splenectomized patients, palpable hepatomegaly is substituted with the same measurement strategy.

**Spleen or liver responses must be confirmed by imaging studies where a ≥35% reduction in spleen volume, as assessed by MRI or CT, is required. Furthermore, a ≥35% volume reduction in the spleen or liver, by MRI or CT, constitutes a response regardless of what is reported with physical examination.

††Symptoms are evaluated by the MPN-SAF TSS.[17] The MPN-SAF TSS is assessed by the patients themselves and this includes fatigue, concentration, early satiety, inactivity, night sweats, itching, bone pain, abdominal discomfort, weight loss, and fevers. Scoring is from 0 (absent/as good as it can be) to 10 (worst imaginable/as bad as it can be) for each item. The MPN-SAF TSS is the summation of all the individual scores (0-100 scale). Symptoms response requires ≥50% reduction in the MPN-SAF TSS.

‡‡Progressive disease assignment for splenomegaly requires confirmation my MRI or computed tomography showing a ≥25% increase in spleen volume from baseline. Baseline values for both physical examination and imaging studies refer to pretreatment baseline and not to posttreatment measurements.

benefit or survival, and that their value as standardized tools of comparison for clinical trials should be approached with caution.

Acknowledgments

The authors acknowledge the key contribution of all IWG-MRT and ELN members who participated in the IWG-MRT annual meetings of 2011 and 2012 in Florence, Italy, as well as the ELN MPN subcommittee conferences at the 2011 and 2012 American Society of Hematology annual meetings in San Diego, CA, and Atlanta, GA, respectively; Prof Rudiger Hehlmann for facilitating the current collaboration and his continued encouragement and support; and Moni and Mary Terner, and the Terner Foundation for providing financial support for the Florence IWG-MRT meetings.

This work was supported by a research grant from Celgene, Incyte, Sanofi, Genentech, NS Pharma, Lilly, and Gilead to R.M.; a research grant from Incyte, Novartis, Gilead, Sanofi to J.G.; and a research grant and honoraria from Incyte, Gilead, and Sanofi and travel support from Incyte, Novartis, and Sanofi to J.G.; and research grants from Novartis, Sanofi, and Shire, and educational materials from Peerview, Medscape, and Articulate Science to C.H.

Authorship

Contribution: A.T., G.B., and T.B. organized and designed the research; A.T., F.C., R.M., F.P., S.V., A.M.V., J.G., B.D., A.P., C.H., R.H., H.G., N.K., J.T., T.B., and G.B. participated in consensus development; and Novartis, Sanofi, Shire to C.H.A.T. wrote the paper.

Conflict-of-interest disclosure: A.T., T.B., A.P., B.D., R.H., F.P., S.V., H.G., J.T., and N.K. declared no conflict of interest; A.M.V. is on the advisory board of Novartis; G.B. and F.C. is on the advisory board of Novartis and Sanofi; R.M. is a consultant for Novartis; J.G. is on the advisory board of Incyte, Novartis, Gilead, and Sanofi; C.H. is on the advisory board of Novartis, Celgene, Sanofi, Gilead, SBio, YM Bioscience, and CTI, and has been a speaker for Shire, Sanofi, and Novartis.

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References

1. Barosi G, Mesa RA, Thiele J, et al. Proposed criteria for the diagnosis of post-polycythemia vera and post-essential thrombocythemia myelofibrosis: a consensus statement from the International Working Group for Myelofibrosis Research and Treatment [letter]. *Leukemia.* 2008; 22(2):437-438.
2. Tefferi A, Vainchenker W. Myeloproliferative neoplasms: molecular pathophysiology, essential clinical understanding, and treatment strategies. *J Clin Oncol.* 2011;29(5):573-582.
3. Cervantes F, Dupriez B, Pereira A, et al. New prognostic scoring system for primary myelofibrosis based on a study of the International Working Group for Myelofibrosis Research and Treatment. *Blood.* 2009;113(13):2895-2901.
4. Cervantes F, Dupriez B, Passamonti F, et al. Improving survival trends in primary myelofibrosis: an international study. *J Clin Oncol.* 2012;30(24): 2981-2987.
5. Mesa RA, Niblack J, Wadleigh M, et al. The burden of fatigue and quality of life in myeloproliferative disorders (MPDs): an international Internet-based survey of 1179 MPD patients. *Cancer.* 2007;109(1):68-76.
6. Barbui T, Carobbio A, Cervantes F, et al. Thrombosis in primary myelofibrosis: incidence and risk factors. *Blood.* 2010;115(4):778-782.
7. Deeg HJ, Gooley TA, Flowers ME, et al. Allogeneic hematopoietic stem cell transplantation for myelofibrosis. *Blood.* 2003;102(12): 3912-3918.
8. Kröger N, Holler E, Kobbe G, et al. Allogeneic stem cell transplantation after reduced-intensity conditioning in patients with myelofibrosis: a prospective, multicenter study of the Chronic Leukemia Working Party of the European Group for Blood and Marrow Transplantation. *Blood.* 2009;114(26):5264-5270.
9. Tefferi A. Primary myelofibrosis: 2013 update on diagnosis, risk-stratification, and management. *Am J Hematol.* 2013;88(2):141-150.
10. Tefferi A, Verstovsek S, Barosi G, et al. Pomalidomide is active in the treatment of anemia associated with myelofibrosis. *J Clin Oncol.* 2009; 27(27):4563-4569.
11. Pardanani A, Gotlib JR, Jamieson C, et al. Safety and efficacy of TG101348, a selective JAK2 inhibitor, in myelofibrosis. *J Clin Oncol.* 2011; 29(7):789-796.
12. Harrison C, Kiladjian JJ, Al-Ali HK, et al. JAK inhibition with ruxolitinib versus best available therapy for myelofibrosis. *N Engl J Med.* 2012; 366(9):787-798.
13. Verstovsek S, Mesa RA, Gotlib J, et al. A double-blind, placebo-controlled trial of ruxolitinib for myelofibrosis. *N Engl J Med.* 2012;366(9): 799-807.
14. Guglielmelli P, Barosi G, Rambaldi A, et al. Safety and efficacy of everolimus, a mTOR inhibitor, as single agent in a phase 1/2 study in patients with myelofibrosis. *Blood.* 2011;118(8):2069-2076.
15. Tefferi A, Barosi G, Mesa RA, et al. International Working Group (IWG) consensus criteria for treatment response in myelofibrosis with myeloid metaplasia, for the IWG for Myelofibrosis Research and Treatment (IWG-MRT). *Blood.* 2006;108(5):1497-1503.
16. Barosi G, Birgegard G, Finazzi G, et al. Response criteria for essential thrombocythemia and polycythemia vera: result of a European LeukemiaNet consensus conference. *Blood.* 2009;113(20):4829-4833.
17. Emanuel RM, Dueck AC, Geyer HL, et al. Myeloproliferative neoplasm (MPN) symptom assessment form total symptom score: prospective international assessment of an abbreviated symptom burden scoring system among patients with MPNs. *J Clin Oncol.* 2012; 30(33):4098-4103.
18. Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the International Working Group for Diagnosis, Standardization of Response Criteria, Treatment Outcomes, and Reporting Standards for Therapeutic Trials in Acute Myeloid Leukemia. *J Clin Oncol.* 2003; 21(24):4642-4649.
19. Cheson BD, Bennett JM, Kantarjian H, et al. Report of an international working group to standardize response criteria for myelodysplastic syndromes. *Blood.* 2000;96(12):3671-3674.
20. Begna KH, Mesa RA, Pardanani A, et al. A phase-2 trial of low-dose pomalidomide in myelofibrosis. *Leukemia.* 2011;25(2):301-304.
21. Verstovsek S, Kantarjian H, Mesa RA, et al. Safety and efficacy of INCB018424, a JAK1 and JAK2 inhibitor, in myelofibrosis. *N Engl J Med.* 2010;363(12):1117-1127.
22. Gale RP, Barosi G, Barbui T, et al. What are RBC-transfusion-dependence and -independence? *Leuk Res.* 2011;35(1):8-11.