References

Body, J.J., Bone, H.G., de Boer, R.H., Stopeck, A., Van Poznak, C., Damiao, R., Fizazi, K., Henry, D.H., Ibrahim, T., Lipton, A., Saad, F., Shore, N., Takano, T., Shaywitz, A.J., Wang, H., Bracco, O.L., Braun, A. & Kostenuik, P.J. (2015) Hypocalcaemia in patients with metastatic bone disease treated with denosumab. *European Journal of Cancer*, **51**, 1812–1821.

Fizazi, K., Lipton, A., Mariette, X., Body, J.J., Rahim, Y., Gralow, J.R., Gao, G., Wu, L., Sohn, W. & Jun, S. (2009) Randomized phase II trial of denosumab in patients with bone metastases from prostate cancer, breast cancer, or other neoplasms after intravenous bisphosphonates. *Journal of Clinical Oncology*, **27**, 1564–1571.

Ikesue, H., Tsuji, T., Hata, K., Watanabe, H., Mishima, K., Uchida, M., Egashira, N., Miyamoto, T., Baba, E., Akashi, K., Takayama, K., Nakanishi, Y., Tokunaga, E., Okamoto, T., Maehara, Y., Yokomizo, A., Naito, S., Kubo, M., Tanaka, M. & Masuda, S. (2014) Time course of calcium concentrations and risk factors for hypocalcemia in patients receiving denosumab for the treatment of bone metastases from cancer. *Annals of Pharmacotherapy*, **48**, 1159–1165.

Lai, F.P., Cole-Sinclair, M., Cheng, W.J., Quinn, J.M., Gillespie, M.T., Sentry, J.W. & Schneider, H.G. (2004) Myeloma cells can directly contribute to the pool of RANKL in bone bypassing the classic stromal and osteoblast pathway of osteoclast stimulation. *British Journal of Haematology*, **126**, 192–201.

Moreaux, J., Hose, D., Kassambara, A., Reme, T., Moine, P., Requirand, G., Goldschmidt, H. & Klein, B. (2011) Osteoclast-gene expression profiling reveals osteoclast-derived CCR2 chemokines promoting myeloma cell migration. *Blood*, **117**, 1280–1290.

Okada, N., Kawazoe, K., Teraoka, K., Kujime, T., Abe, M., Shinohara, Y. & Minakuchi, K. (2013) Identification of the risk factors associated with hypocalcemia induced by denosumab. *Biological &/and Pharmaceutical Bulletin*, **36**, 1622–1626.

Raje, N., Terpos, E., Willenbacher, W., Shimizu, K., Garcia-Sanz, R., Durie, B., Legiec, W., Krejci, M., Laribi, K., Zhu, L., Cheng, P., Warner, D. & Roodman, G.D. (2018) Denosumab versus zoledronic acid in bone disease treatment of newly diagnosed multiple myeloma: an international, double-blind, double-dummy, randomised, controlled, phase 3 study. *The Lancet. Oncology*, **19**, 370–381.

Terpos, E., Szydlo, R., Apperley, J.F., Hatjiharissi, E., Politou, M., Meletis, J., Viniou, N., Yataganas, X., Goldman, J.M. & Rahemtulla, A. (2003) Soluble receptor activator of nuclear factor kappaB ligand-osteoprotegerin ratio predicts survival in multiple myeloma: proposal for a novel prognostic index. *Blood*, **102**, 1064–1069.

Vij, R., Horvath, N., Spencer, A., Taylor, K., Vadhan-Raj, S., Vescio, R., Smith, J., Qian, Y., Yeh, H. & Jun, S. (2009) An open-label, phase 2 trial of denosumab in the treatment of relapsed or plateau-phase multiple myeloma. *American Journal of Hematology*, **84**, 650–656.

Witteveen, J.E., van Thiel, S., Romijn, J.A. & Hamdy, N.A. (2013) Hungry bone syndrome: still a challenge in the post-operative management of primary hyperparathyroidism: a systematic review of the literature. *European Journal of Endocrinology*, **168**, R45–R53.

Comments on pre-fibrotic myelofibrosis and how should it be managed

We read with great interest the recent paper by Curto-Garcia *et al* (2018) regarding the problems and pitfalls concerning the diagnosis of pre-fibrotic myelofibrosis (pre-PMF) and appreciate that the authors recognize this subtype of myeloproliferative neoplasm (MPN). While the article addresses a very timely and important topic with high impact for clinical practice and management of patients, we would like to highlight and discuss a few critical issues. The controversies underlying the debates concerning pre-PMF, which had been included in the 2001 World Health Organization (WHO) myeloid classification scheme as "chronic idiopathic myelofibrosis pre-fibrotic stage" (Jaffe *et al*, 2001), derive from multiple reasons that will be briefly discussed below.

It is of note that, although bone marrow (BM) morphology remains the cornerstone of diagnosis, the WHO classification envisions a strictly integrated approach, i.e. a multi-disciplinary process including clinical and molecular genetic findings. In this context, baseline clinical data and treatment-naïve representative BM biopsy specimens are mandatory (Swerdlow *et al*, 2017) to facilitate the evaluation of BM features according to standardized parameters (Thiele *et al*, 2011). As has been pointed out, diagnostic reliability compared with other haematological disorders may be problematic concerning a more limited intra-and inter-observer reproducibility. Referring to the case reports and abstracts of pre-PMF, accurate fibre grading (WHO 0–1/3) is essential (e.g. a simple $\geq$ grade 1 is not adequate). The main clinical and haematological variables and, very importantly, outcome, have been shown to correlate with fibrosis grading (Guglielmelli *et al*, 2017). The problems and pitfalls that can be encountered when including the role of BM morphology in the crucial differentiation between pre-PMF and essential thrombocythaemia (ET), have been highlighted previously (Thiele *et al*, 2011; Gisslinger *et al*, 2016). Therefore, we strongly recommend to reclassify the initial BM biopsies derived from older cohorts according to 2016 WHO criteria, particularly in patients who were classified as ET based on previous diagnostic criteria. Rumi *et al* (2017) reported that, of the 358 "old" ET cases, 268 (75%) were reclassified as ET, 25 (7%) as unclassifiable and 65 (18%) as pre-PMF. The latter patients had a higher risk of overt myelofibrosis (9·7% vs. 0% at 10 years) compared to those reclassified as WHO-defined ET.

The clinical presentation of pre-PMF patients appropriately diagnosed according to the revised WHO definition (Swerdlow

et al, 2017) reveals a high degree of consistency between clinical data, BM morphology and presence of the following findings :borderline anaemia (25%), leucocytosis (51%), elevated lactate dehydrogenase (79%) and palpable splenomegaly (45)%; more than 90% of pre-PMF cases initially show one or more of the above features that represent minor diagnostic criteria compared to about 48% of ET patients (Jeryczynski *et al*, 2017). Constitutional symptoms were reported in only 20%, significantly lower than in overt PMF (34%; Guglielmelli *et al*, 2017). It should be emphasised that, except for establishing clonal evolution, molecular data or cytogenetic findings are not useful to differentiate pre-PMF from ET.

As has been emphasised, prognosis is significantly different between pre-PMF and ET. When regarding data from several large studies on 1383 adult patients with pre-PMF vs. 2125 patients with WHO-defined ET, the overall median, cumulative or relative and sex-/age-adjusted relative survival revealed significant differences, with ET patients having almost double the overall median survival of pre-PMF patients (Thiele *et al*, 2011; Guglielmelli *et al*, 2017) or a 10/15-year cumulative incidence of death (Barbui *et al*, 2011). By using the five independent predictors of inferior survival (age >65 years, haemoglobin <100 g/l, leucocyte count >25 $\times$ 10^9/l, circulating blasts >1%, constitutional symptoms), Guglielmelli *et al* (2017) calculated that 48% of pre-PMF patients were in the low-risk group, 40% in the intermediate 1+ plus 2 group and only 12% were included in the high risk group, which was significantly different from overt PMF.

Regarding therapy, given that the majority of patients lie within the International Prognostic Scoring System lower prognostic group, observation alone can be recommended. Patients with intermediate risk may require a symptom-driven treatment for anaemia, splenomegaly or constitutional symptoms. On the other hand, high risk patients should be treated as overt PMF, as has been recently reviewed by Finazzi *et al* (2018). A pragmatic approach to address the risk of bleeding and thrombosis includes: no treatment or low-dose aspirin in asymptomatic patients; aspirin or oral anticoagulation if previous arterial or venous thrombosis, and hydroxycarbamide as first-line cytoreduction in case of thrombocytosis or leucocytosis.

Additionally, we have to address the differences in published cohorts of pre-PMF patients that may be caused by the method of recruitment. The first bias is the retrospective selection from archived material and reclassification. The second is that selection may be focused either on ET or PMF cases derived from archive material and, rarely, initially-presenting patients. Consequently, cohorts with a more "ET-like" phenotype (high platelet counts, low percentage of patients with WHO fibrosis grade 1 *versus* groups with a more "PMF-like" phenotype (lower platelet counts, high percentage of WHO fibrosis grade 1 may be encountered. Concerning transformation to acute myeloid leukaemia, Barbui *et al* (2011) reported an incidence of 5·8% at 10 years, including 24% patients with WHO fibrosis grade 1, in contrasting with Guglielmelli *et al* (2017), who reported an incidence of 12%, including 72% patients with fibrosis grade 1. In contrast, Jeryczynski *et al* (2017) investigated the whole spectrum of routinely presenting 170 pre-PMF patients, including 14·6% of cases with platelet counts <450 $\times$ 10^9/l and grade 1 fibrosis in 35% of cases. Pre-PMF patients that present with initial reticulin fibrosis may contribute to a more aggressive course of disease. The cumulative incidences of progression to overt PMF at 10 years were calculated to reach 31·5% (Jeryczynski *et al*, 2017). These data are substantially higher compared to previously published results (12·3% and 9·7% at 10 years), respectively, mostly recruited from ET-archived cases (Barbui *et al*, 2011; Rumi *et al*, 2017).

In conclusion, the present situation calls for multicentre prospective studies on pre-PMF with a centralized pathology review of the BM biopsy specimens by experts, to improve diagnostic reliability and provide prospective analysis of phenotype presentation, clinical course and outcome.

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Conflict of interest

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References

Barbui, T., Thiele, J., Passamonti, F., Rumi, E., Boveri, E., Ruggeri, M., Rodeghiero, F., d'Amore, E.S., Randi, M.L., Bertozzi, I., Marino, F., Vannucchi, A.M., Antonioli, E., Carrai, V., Gisslinger, H., Buxhofer-Ausch, V., Müllauer, L., Carobbio, A., Gianatti, A., Gangat, N., Hanson, C.A. & Tefferi, A. (2011) Survival and disease progression in essential thrombocythemia are significantly influenced by accurate morphologic diagnosis: an international study. *Journal of Clinical Oncology*, **29**, 3179–3184.

Curto-Garcia, N., Ianotto, J.-C. & Harrison, C.N. (2018) What is pre-fibrotic myelofibrosis and how should it be managed in 2018? *British Journal of Haematology*, **183**, 23–34.

Finazzi, G., Vannucchi, A.M. & Barbui, T. (2018) Prefibrotic myelofibrosis: treatment algorithm. *Blood Cancer Journal*, **8**, 104.

Gisslinger, H., Jeryczynski, G., Gisslinger, B., Wölfler, A., Burgstaller, S., Buxhofer-Ausch, V., Schalling, M., Krauth, M.-T., Schiefer, A.-I., Kornauth, C., Simonitsch-Klupp, I., Beham-Schmid, C., Müllauer, L. & Thiele, J. (2016) Clinical impact of bone marrow morphology for the diagnosis of essential thrombocythemia: comparison between the BCSH and the WHO criteria. *Leukemia*, **30**, 1126–1132.

Guglielmelli, P., Pacilli, A., Rotunno, G., Rumi, E., Rosti, V., Delaini, F., Maffioli, M., Fanelli, T., Pancrazzi, A., Pietra, D., Salmoiraghi, S., Mannarelli, C., Franci, A., Paoli, C., Rambaldi, A., Passamonti, F., Barosi, G., Barbui, T., Cazzola, M. & Vannucchi, A.M.; AGIMM Group. (2017) Presentation and outcome of patients with 2016 WHO diagnosis of prefibrotic and overt primary myelofibrosis. *Blood*, **129**, 3227–3236.

Jaffe, E.S., Harris, N.L., Stein, H. & Vardiman, J.W.E. (eds.) (2001) *World Health Organization Classification of Tumours. Pathology and Genetics of Tumours of Haematopoietic and Lymphoid Tissues*, 1st edn. International Agency for Research on Cancer Press, Lyon, France.

Jeryczynski, G., Thiele, J., Gisslinger, B., Wölfler, A., Schalling, M., Gleiß, A., Burgstaller, S., Buxhofer-Ausch, V., Sliwa, T., Schlögl, E., Geissler, K., Krauth, M.-T., Nader, A., Vesely, M., Simonitsch-Klupp, I., Müllauer, L., Beham-Schmid, C. & Gisslinger, H. (2017) Pre-fibrotic/early primary myelofibrosis vs. WHO-defined essential thrombocythemia: the impact of minor clinical diagnostic criteria on the outcome of the disease. *American Journal of Hematology*, **92**, 885–891.

Rumi, E., Boveri, E., Bellini, M., Pietra, D., Ferretti, V.V., Sant'Antonio, E., Cavalloni, C., Casetti, I.C., Roncoroni, E., Ciboddo, M., Benvenuti, P., Landini, B., Fugazza, E., Troletti, D., Astori, C. & Cazzola, M. (2017) Clinical course and outcome of essential thrombocythemia and prefibrotic myelofibrosis according to the revised WHO 2016 diagnostic criteria. *Oncotarget*, **8**, 101735–101744.

Swerdlow, S.H., Campo, E., Harris, N.L., Jaffe, E.S., Pileri, S.A., Stein, H. & Thiele, J. (eds.) (2017) *WHO Classification of Tumours of Haematopoietic and Lymphoid Tissues*, 4th edn. International Agency for Research on Cancer Press, Lyon, France.

Thiele, J., Kvasnicka, H.M., Müllauer, L., Buxhofer-Ausch, V., Gisslinger, B. & Gisslinger, H. (2011) Essential thrombocythemia versus early primary myelofibrosis: a multicenter study to validate the WHO classification. *Blood*, **117**, 5710–5718.

Index of Pain Experience in Sickle Cell Anaemia (IPESCA): development from daily pain diaries and initial findings from use with children and adults with sickle cell anaemia

Pain burden assessments are essential to evaluate the effectiveness of interventions in sickle cell anaemia (SCA) treatment trials. Number of days in pain or number of hospital admissions are commonly utilised but these measures overlook additional important clinical information captured in complex pain diaries that are challenging to quantify and summarise. We created a simple, intuitive composite index (Index of Pain Experience in Sickle Cell Anaemia [IPESCA]), which reflects frequency as well as location, intensity and type of pain.

The sample included 61 children and adults screened for the Prevention of Morbidity in Sickle Cell Anaemia (POMS) phase-II randomised controlled trial (Howard *et al*, 2018). At screening visit, patients completed a paper pain diary for 14 consecutive days, which included shading locations of pain on a body map, circling words to describe their pain and choosing a 0–10 numerical rating of pain intensity. The body map diagram (von Baeyer *et al*, 2011) was divided into 18 specific areas, and the widespread pain index (WSPi) (Zempsky *et al*, 2017) comprised the total number of body locations in pain over the two-week period. Eight of 21 descriptor words were classified as 'neuropathic' (*e.g.* aching, stabbing, numb, shooting, pricking, burning, penetrating, radiating) (Wilkie *et al*, 2010). IPESCA is a novel summary measure, consisting of four components: WSPi, maximum persistence of pain, defined as the total number of days in pain at any one location, total number of neuropathic words chosen, and mean of daily average pain intensity. The components were equally weighted using this equation:

$$f(x) = \frac{(\max[new] - \min[new])(x - \min[original])}{\max[original] - \min[original]} + \min[new]$$

and scaled to range 0–0·25 to create a summed index (range 0–1).

Patients also completed the validated Sickle Cell Pain Burden Inventory-Youth (SCPBI-Y) questionnaire (Zempsky *et al*, 2013), which assesses the past month's impact of pain on physical, social and emotional aspects of daily function. The SCPBI-Y was completed at the screening visit and at randomisation visit 30 days later, together representing the previous 2 months of pain burden.

Analyses were performed using R version 3.3.2 (www.r-project.org). Demographics were compared using the t-test for continuous variables, the chi-squared test or Fisher's exact test for categorical variables. IPESCA was tested for skewness and kurtosis using the R 'moments' package (Komsta &