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Invited review

Myeloproliferative neoplasms 2012: The John M. Bennett 80th birthday anniversary lecture

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ABSTRACT

Polycythemia vera, essential thrombocythemia and primary myelofibrosis constitute the *BCR-ABL1*-negative myeloproliferative neoplasms. In this communication, I will provide an overview on their histopathology, cytogenetic findings and associated mutations, as well as summarize recent advances that have changed our approach to their diagnosis and treatment. Also included in the current review are (i) indications for ordering *JAK2* or *MPL* mutation analysis and result interpretation, (ii) new international prognostic scoring systems, and (iii) risk-adapted therapy including the therapeutic role of immunomodulatory drugs and JAK inhibitors.

Contents

1. Introduction

The World Health Organization (WHO) classification system for myeloid malignancies distinguishes myeloproliferative neoplasms (MPN) from both myelodysplastic syndromes (MDS) and MDS/MPN overlap (Fig. 1) [1]. At present, eight clinicopathologic entities are listed under the WHO category of MPN and they include the so-called "*BCR-ABL1*-negative MPN": polycythemia vera (PV), essential thrombocythemia (ET) and primary myelofibrosis (PMF) [2]. Stem cell-derived clonal myeloproliferation, recurrent cytogenetic or submicroscopic genetic alterations and a variable risk of leukemic transformation (LT) characterize these MPN [3]. Unlike the case with chronic myelogenous leukemia (CML), the disease initiating mutation(s) in *BCR-ABL1*-negative MPN has not been identified and our knowledge is equally incomplete regarding the molecular events leading to disease transformation into acute leukemia or post-ET/PV MF [3].

2. Histopathology

Bone marrow (BM) morphology is the cornerstone of diagnosis and disease classification in MPN. The 2008 revised WHO system [1] includes five categories of myeloid malignancies: MPN, acute myeloid leukemia (AML), MDS, "MDS/MPN" overlap, and

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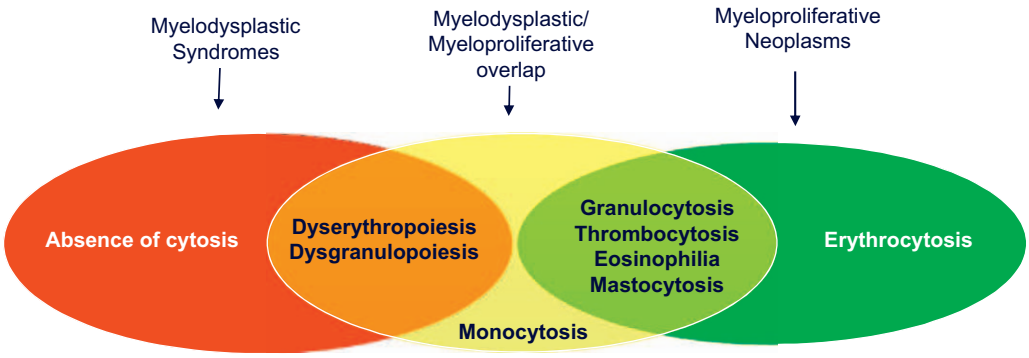

Fig. 1. World Health Organization Classification of chronic myeloid malignancies. *Abbreviations*: MPN, myeloproliferative neoplasms; MPN-U, MPN unclassifiable.

"*PDGFRα/β*- or *FGFR1*-rearranged myeloid/lymphoid neoplasms associated with eosinophilia". MPN is distinguished from AML by the absence of ≥20% peripheral blood (PB) or BM blasts and from MDS and MDS/MPN by the absence of dysgranulopoiesis, dyserythropoiesis or monocytosis ($\geq 1 \times 10^9$/L). The MDS/MPN provisional category of "refractory anemia with ring sideroblasts and thrombocytosis (RARS-T)" is phenotypically the closest to MPN and is characterized by the presence of dyserythropoiesis, ≥15% ring sideroblasts, megakaryocyte morphology that is similar to that seen in MPN, and platelet count $>450 \times 10^9$/L. RARS-T also resembles MPN in terms of *JAK2V617F* mutational frequency (~50%) [4] but the two are significantly different in their *SF3B1* mutational frequencies (~3% in ET, 7% in PMF, 67% in RARS-T, 73% in RARS and 37% in RCMD-RS) [5–8].

In general, BM in MPN displays trilineage myeloid hyperplasia, megakaryocyte clusters and reticulin fibrosis [9]. Megakaryocyte morphology is the most useful not only in distinguishing MPN from other related myeloid malignancies but also in making specific diagnosis within MPN. Megakaryocytes in ET are large, hyperlobulated and mature-appearing whereas those in PMF (including prefibrotic PMF) display abnormal maturation with hyperchromatic and irregularly folded bulky nuclei. In PV, megakaryocytes are pleomorphic with both large and small forms, but without maturation defects. Trilineage myeloproliferation is most pronounced in PMF but is also prominent in PV but not in ET. In fibrotic PMF, both reticulin and collagen fibrosis are present and often associated with osteosclerosis. Low but not high grade reticulin fibrosis can also be seen in ET and PV whereas fibrosis might be minimal in prefibrotic/early PMF [10–13]. The distinction between prefibrotic/early PMF and ET is prognostically relevant [13].

3. Karyotype

By definition, the Philadelphia chromosome (and *BCR-ABL1*) is absent in PV, ET and PMF. However, other recurrent cytogenetic abnormalities are seen in approximately 33% of patients with PMF [14], 11% in PV [15] and 7% in ET [16]. The types of abnormalities seen in these three *BCR-ABL1*-negative MPN are similar and include del(20q), del(13q), +8, +9, chromosome 1 abnormalities, and chromosomes 5 and 7 abnormalities. Among these, +9 and del(13q) are relatively specific to MPN whereas the others are also seen in MDS [17]. Chromosomal breakpoint regions seen with del(20q) include q11.2-13.1, with del(13q) q12-22 and with chromosome 1 anomalies q10-25/p10-31. To date, prognostic relevance for karyotype has been demonstrated in PMF [18,19] and PV [20] but not in ET [16].

According to one of the largest cytogenetic studies in PMF ($n = 433$), an abnormal karyotype was documented in 36% ($n = 158$) of the patients [21]. Among the latter, 109 (69%) constituted sole abnormalities, 23 (15%) two abnormalities and 26 (17%) ≥three abnormalities. The most frequent sole abnormality was 20q− (28%) whereas other sole abnormalities, in decreasing order of frequency, included +8, 13q−, chromosome 1 translocation/duplication, +9 and −7/7q−. Prognostic correlations identified +8, i(17q), −5/5q−, 12p−, 11q23 rearrangement or inv(3) as being unfavorable even when they occur as isolated abnormalities. Complex or monosomal karyotype [22] were also prognostically unfavorable and a more recent study identifies monosomal karyotype, i(17q) and inv(3) as being the most detrimental in this regard [18]. Significantly better survival was seen in patients with normal karyotype as well as those with sole abnormalities of 13q−, 20q−, +9, and chromosome 1 translocations/duplications [19].

4. Mutations

The discovery of *JAK2V617F* (an activating *JAK2* mutation) has been the single most important contribution to the field of MPN in recent times [3]. Almost all patients with PV harbor a *JAK2* mutation that includes *JAK2V617F* (exon 14) in ~97% of the patients and *JAK2* exon 12 mutation in ~2% [23,24]; the remaining 1% are currently believed to carry other JAK/STAT-relevant mutations such as those involving *LNK* [25]. *JAK2V617F* also occurs in at least 50% of patients with ET or PMF and displays phenotypic correlations with older age, higher hematocrit, leukocytosis, and lower platelet count [24]. *JAK2V617F* has also been associated with an increased risk of arterial thrombosis in ET and a lower risk of post-ET MF [13,26]. However, the presence of *JAK2V617F* has not been consistently associated with survival or LT in ET, PV or PMF [3,13,24,27]. Mitotic recombination results in *JAK2V617F* homozygosity that is often seen in PV and PMF but usually not in ET and has been associated with pruritus and fibrotic transformation in PV [27]. Interestingly, a lower mutant allele burden was significantly associated with worse survival in PMF, by two independent groups [28,29]. *JAK2* mutations other than *JAK2V617F* are infrequent in MPN and amongst them, *JAK2* exon 12 mutations are the most frequent. The latter has so far been demonstrated in PV only and associated with predominantly erythroid myelopoiesis, subnormal serum erythropoietin level, younger age at diagnosis, and similar prognosis to that of *JAK2V617F*-positive PV [30].

Mutations involving genes other than *JAK2* are found in less than 20% of patients with MPN and are not necessarily mutually exclusive of *JAK2V617F* or each other [3]. These include *MPL* (myeloproliferative leukemia virus oncogene; exon 10 and occurring in ~3% in ET and 10% in PMF) *LNK* (a membrane-bound adaptor protein; usually involving exon 2 and seen in <1% in PV, ET or PMF), *TET2* (TET oncogene family member 2; involving several exons and occurring in ~5% in ET and 15–20% in PV or PMF), *ASXL1* (additional sex combs-like 1; often involving exon 12 and seen in ~5% in ET and 20% in PMF), *IDH1/IDH2* (isocitrate dehydrogenase; involving exon 4 and seen in <5% in PMF and <3% in PV or ET), *EZH2* (enhancer of zeste homolog 2; involving several exons and seen in