Do We Need Biological Studies for Patient Management?

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2.1 Introduction

Management decisions for patients with MPN vary between the different disease entities and must include of course the achievement of an accurate diagnosis. For patients with essential thrombocythaemia (ET) and polycythaemia vera (PV), initial disease management most commonly focuses upon preventing thrombotic events, ideally without exacerbating the risk of bleeding. However, a further important management goal for both clinicians and patients is to reduce the risk of progression or transformation to more destructive disease entities. In this respect, clinicians will target treatment to reduce the risk of transformation to acute myeloid leukaemia (AML) and myelodysplasia (MDS). There is, thus far, no clear evidence that specific treatment can reduce the risk of transformation to post-ET or post-PV myelofibrosis (MF). For example, although studies of French patients entered into Polycythemia Vera Study Group (PVSG) trials suggest that hydroxycarbamide treatment and elevated platelet count may increase the risk of post-PV MF (Najean and Rain 1997), the PT-1 trial in ET suggests that risks of post-ET MF may be greater with anagrelide than hydroxycarbamide (Harrison et al. 2005). However, if a biological marker for accelerated risk of transformation was identified, then this would potentially facilitate better targeted care. For patients with established MF, whether arising de novo as primary MF (PMF) or following ET or PV, the risk of thrombosis and haemorrhage subsists. Indeed, a recent study (Barbui et al. 2010)

T. Barbui and A. Tefferi (eds.), *Myeloproliferative Neoplasms*, Hematologic Malignancies,
DOI 10.1007/978-3-642-24989-1_2,

suggests the risk of thrombosis in PMF is very similar to that for ET. More pressing in the management of MF, however, is the need to accurately separate patients by likely prognosis, and in this regard, biological studies may prove to contribute significantly. As we shall discuss in this chapter, there is also potential to use additional biological studies or markers to orientate treatment strategies and, indeed, to design novel therapeutics against disease-specific features (e.g. increased JAK2 activation), as well as to monitor response.

2.2 Attributes of Biological Studies

Research findings are often made by a small group of investigators either in the laboratory or with a specific patient cohort. There are a number of potential difficulties inherent in the process of translating these findings into a global health-care strategy. Clinicians will need to interpret and apply research data appropriately. For example, a positive result for the *JAK2* V617F mutation in a patient with a thrombocytosis does not always imply the presence of ET, PV or PMF. Alternative diagnostic entities may present this picture, such as chronic myelomonocytic anaemia or an MDS variant such as refractory anaemia with sideroblasts and thrombocytosis. Biological markers should therefore provoke careful evaluation in the context of history, examination and other investigations.

A further important factor is that the biological study or test should be sufficiently robust and reproducible in different clinical settings. This should be established prior to widespread adoption in clinical practice, and thenceforth in the longer term should be subject to ongoing quality control. In the UK, the National External Quality Assurance Scheme (NEQAS) serves this purpose by providing regular assessment exercises, peer-group comparison of results and assistance in the case of persistently unsatisfactory performance. These concerns regarding reliability and reproducibility are relevant for novel biological studies which can be undertaken by most laboratories as well as more specialised tests which are performed only in specialist centres either due to low volume, cost, or technical requirements.

2.3 Markers for Diagnosis

Diagnostic criteria for MPN were first developed under the auspices of the PVSG, and until the discovery of the *JAK2* V617F (James et al. 2005), mutation generally required a cardinal myeloproliferative feature and the exclusion of other causative mechanisms. For instance, a diagnosis of ET would typically involve a finding of thrombocytosis, followed by the exclusion of a reactive cause or another myeloid disease (MDS, PV, PMF, etc.) (Murphy et al. 1986). The World Health Organization (WHO) diagnostic criteria first introduced the concept of characteristic bone marrow histological features which would support a diagnosis of an MPN. These criteria have subsequently been modified to incorporate molecular markers such as *JAK2* V617F, *MPL* mutations and *JAK2* exon 12 mutations (Tefferi et al. 2009). The inclusion of these molecular markers greatly improves both the speed and certainty of diagnosis, thus having a positive impact upon patient management. However, it should be emphasised that these studies are incorporated into diagnostic criteria and do not replace them. Although over 95% of patients with PV will have one or more *JAK2* mutations, only 50–60% of patients with ET or PMF will have *JAK2* or *MPL* mutations. Furthermore, the robust application of diagnostic criteria should be followed for all patients, regardless of the results of molecular markers, to exclude concomitant conditions and the rare possibility of a false-positive molecular test. A significant number of additional molecular abnormalities have been defined, including mutations of *TET2, ASLXI, EZLH, IDH* and *Lnk* (as discussed in Chap. 1). These mutations are not generally employed as diagnostic markers in routine practice, and many are not as specific for MPN as *JAK2* and *MPL* mutations. The predisposition afforded by the *JAK2* 46/1 (GGCC) haplotype (Jones et al. 2009) is also not of routine diagnostic utility, nor should it be used to screen family members for potential to develop disease.

Under current WHO diagnostic criteria, it remains possible to make a robust diagnosis of MPN without performing tests beyond a full blood count, blood film and bone marrow biopsy. Certain patients with PV may require in addition

an erythropoietin level and red cell mass test, whereas confirmation of a diagnosis of PMF may necessitate measurement of lactate dehydrogenase (LDH) levels. Hence biological studies are not imperative to achieve a diagnosis of MPN, but they are in routine and widespread use. A particular clinical scenario where testing for *JAK2* and *MPL* mutations may be of significant diagnostic utility is in the case of a patient with unexplained splanchnic vein thrombosis, where an occult MPN is a common predisposing factor and classical blood count abnormalities may be masked by haemodilution (Patel et al. 2006).

2.4 Prognosis and Disease Transformation

The prognosis for patients with MPN is variable; for patients with ET and PV, it is likely to exceed 20 years, whereas for PMF, the median prognosis is 10 years (Barbui et al. 2011). Leukaemic transformation is a poor prognostic factor for all diseases and is generally fatal, with the exception of a small minority of patients who remit with intensive chemotherapy and are able to undergo allogeneic transplantation (Mesa et al. 2005). For PMF, a number of prognostic scores, including the IPSS (Cervantes et al. 2009) and the dynamic IPSS (Passamonti et al. 2010; Gangat et al. 2011), have been developed and are discussed further in chapters 7 and 14 of this book. These prognostic evaluations do not at present include biological studies apart from cytogenetics. There are variable reports for the prognostic implication of allelic burden for *JAK2* V617F in PMF. Most recent publications suggest a poor prognosis with low allelic burden (Tefferi et al. 2008). However, the difficulties in quality assurance of this test, and the strength of the IPSS and dynamic IPSS, have precluded the inclusion of allelic burden as a standard prognostic marker.

For patients with ET and PV, prognosis is largely determined by the number of thrombotic complications (Lengfelder et al. 1998), and the utility of biological studies in defining the risk of their occurrence is discussed below. Transformation to MF or AML portends a markedly worse prognosis, but novel biological studies do not contribute significantly to this assessment. Elevated *JAK2* V617F allelic burden has been associated with features of more advanced disease in PV, but it is not known whether it is predictive of progression in disease status. Of interest are reports that in patients with *JAK2* V617F mutation in chronic phase disease, leukaemic blasts in at least a half of cases are negative for the mutation (Campbell et al. 2006; Theocharides et al. 2007).

2.5 Thrombosis or Haemorrhage

Thrombotic events are particularly common clinical manifestations of MPN, and define risk stratification for patients with ET and PV. For these patients, the dominant predictors for thrombosis are age and a prior event, with increasing evidence of a role for leucocytosis (Barbui et al. 2011). For patients with PMF, recent data suggest that these patients do suffer from an increased risk of fatal and non-fatal cardiovascular events at a rate of 1.75% per patient-year, which is similar to that for patients with ET (Barbui et al. 2010). Risks for thrombosis in patients with PMF include age over 60 years and the presence of *JAK2* V617F, particularly for patients with leucocytosis ($>15 \times 10^9$/L). Recent biological studies at present do not contribute further to the assessment of thrombotic risk, although a meta-analysis does suggest an increased risk of thrombosis in *JAK2* V617F–positive patients with ET (Dahabreh et al. 2009). Haemorrhage is less frequent than thrombosis and is associated with extreme thrombocytosis, aspirin use and acquired von Willebrand's disease (Budde et al. 1984).

2.6 Treatment Strategy

Once a specific instance of MPN has been disease-risk stratified and associated health conditions taken into account, is there any impact of current biological studies in further deciding which particular therapy a patient would most benefit from? At the present time, there is no established evidence to advocate a particular therapeutic option on the

basis of a patient's mutation status. A subgroup analysis of the PT-1 study has suggested that ET patients with the *JAK2* V617F mutation were less likely to have arterial thrombosis when treated with hydroxycarbamide and aspirin than with anagrelide and aspirin, whereas for patients without the *JAK2* V617F mutation, there was no difference in arterial thrombotic events when treated with either drug combination (Campbell et al. 2005). Given the association of *JAK2* V617F mutation with leucocytosis (Cheung et al. 2006), and the correlation both between leucocytosis and *JAK2* V617F mutation and between leucocytosis and thrombosis, the pan-myelosuppressive action of hydroxycarbamide compared with the specific action of anagrelide to lower the platelet count suggests a mechanism to explain this observation. This finding has not been tested by other authors and has not translated into a general recommendation.

More recently, it is of significant interest that emerging data with regard to JAK inhibitor therapy, as a treatment initially for PMF, suggest that these agents appear to be equally effective in patients regardless of whether they have a *JAK2* mutation or not (Verstovsek et al. 2010). Thus, even with novel therapies, biological studies are not yet required to tailor treatment choice.

2.7 Monitoring Response

Response criteria to guide the management of ET, PV and PMF have been drawn up by expert consensus through the European Leukemia Net (ELN) (Barosi et al. 2009), European Myelofibrosis Network (EUMNET) (Barosi et al. 2005) and International Working Group for Myelofibrosis Research and Therapy (IWG-MRT) (Tefferi et al. 2006). Most recently, critical concepts and management recommendations have been developed by the ELN (Barbui et al. 2011). In general, these response criteria refer to control of blood counts, relief of anaemia or moderation of transfusion dependency, reduction in organomegaly (particularly splenomegaly), control of symptoms and resolution of bone marrow abnormalities on trephine biopsy. The presence or resolution of cytogenetic abnormalities is not generally referenced in these criteria. The only response criteria to reference biological studies are the ELN consensus criteria for response in ET and PV which include molecular response (Barosi et al. 2009). Here, the definition of molecular response is based on quantitative allele burden of the specific molecular abnormalities (e.g. *JAK2* V617F, exon 12 and *MPL* mutations) and acknowledges that sensitivity of detection varies according to the method used and that significant variation in consecutive samples from an individual patient is possible even without therapy. Consequently, the concept of molecular response is defined on the basis of detection levels, and partial response is applied only to patients with a baseline value of mutant allele burden greater than 10%. Implicit in these statements is the admission of technical difficulties in assessing molecular response.

Recently, the value of monitoring *JAK2* V617F and *MPL* 515L allele burden has been demonstrated in the setting of bone marrow transplant where monitoring of minimal residual disease guides the use of post-transplant immunotherapy (Kroger et al. 2007); the same group failed to find correlation with circulating CD34 cell number as a marker of minimal residual disease or predictor of relapse (Alchalby et al. 2011). Interestingly with regard to *JAK2* V617F allele burden, these authors conclude that knowledge of the *JAK2* V617F–mutated status, but not allele frequency, yields improved survival and that rapid clearance after allograft reduces the risk of relapse (Alchalby et al. 2010). For patient management outside the setting of transplantation, the clinical value of monitoring mutated allele burden has not been validated. For example, although Kildajian and colleagues demonstrated that Pegasys therapy in 40 newly diagnosed patients with PV was able to significantly reduce *JAK2* V617F allele burden, there was no clearly demonstrated reduction in thrombosis as the study had no control group and was not designed to demonstrate this endpoint (Kiladjian et al. 2006). A larger trial in progress is required to elucidate whether biologic modification translates into clinically meaningful response such as reduction in risk of thrombosis or disease evolution.

Thus, the use of biological studies to monitor response is currently restricted to the context of post-transplant immunotherapy and to clinical trials designed to assess the value of newer agents for disease management.

2.8 Summary and Conclusion

Significant advances in our understanding of the MPN have been underpinned by biological discoveries. In this chapter, we have discussed their current utility in patients' management, addressing the question "Do we need biological studies for patient management?" At present, we have identified that the main utility for these studies is in achieving a diagnosis, although a diagnosis may be achieved without recourse to these sometimes expensive tests. Advances in the field are at a stage where we are beginning to consider the use of minimal residual disease monitoring especially in the post-transplant setting. We have much to learn before these studies will fully complement accurate clinical evaluation and standard laboratory tests.

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http://www.springer.com/978-3-642-24988-4

Myeloproliferative Neoplasms
Critical Concepts and Management
Barbui, T.; Tefferi, A. (Eds.)
2012, VIII, 240 p., Hardcover
ISBN: 978-3-642-24988-4