

Venue: PYRAMID 1
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1030-1145 hr

Symposium 3B: Risk management in myeloproliferative disorders

S3B-1. How useful is the WHO Classification of the myelodysplastic syndromes

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The WHO classification of the myelodysplastic syndromes can be viewed as an evolutionary development of the French-American-British (FAB) system of the early 1980's. The advantages of the FAB system were its wide acceptance and clinical usefulness. It can be seen as relatively "low tech", relying on good quality blood and marrow staining and morphology. The application of this system was easily exported with an acceptable degree of reproducibility. The WHO classification of the new millennium (2001) built upon these advantages as well as attempting to resolve some of the "problems" of its predecessor and incorporate the rapidly expanding developments of genetics and molecular genetics in the haematological malignancies. Significant advances of the WHO classification include the recognition of the relatively good prognostic significance of the "erythroid-restricted" disorders (RA & RARS) whilst at the same time delineating the adverse prognostic significance of cytopenias associated with multilineage dysplasia (RCMD). The prognostic significance of marrow blast percentage was recognised by the splitting of the REAB subtype (I & II) and the abandonment of the RAEB-t in favor of a redefinition of acute leukaemia (>20% marrow blasts). By analogy with developments in the genetics of AML, a "new" disease with defined by its genetic abnormality, the 5q- syndrome. AML cases in the context of pre-existing MDS were also recognised as a particular clinical grouping with a generally poor outcome. Finally, the overlap with the myeloproliferative disorders was recognised by creating such an overlap category (MDS/MPD), which now contained CMML. A number of recent publications have confirmed the clinical usefulness of the WHO classification especially when combined with cytogenetics and it will be of interest to see whether advances in molecular genetics, including gene profiling, further refine our understanding of these diseases.

S3B-2. Thrombosis risk in the chronic myeloproliferative disorders

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The chronic myeloproliferative disorders, polycythemia vera (PV), idiopathic myelofibrosis (IMF) and essential thrombocytosis (ET) are customarily classified together because they share in common many features, including origin in a multipotent stem cell, expression of mutations in JAK2 and MPL, overproduction of one or more of the formed elements of the blood, clonal dominance, marrow hypercellularity and megakaryocyte dysplasia, abnormalities of chromosomes 1,8,9,13 and 20, growth factor-independent in vitro colony formation, extramedullary hematopoiesis, myelofibrosis and transformation to acute leukemia at varying rates. Clinically, a propensity for thrombosis is a major source of morbidity in PV and ET, while hemorrhage, usually due to platelet dysfunction, is a feature of all three illnesses. Indeed, in early studies, thrombosis was observed as a presenting feature in 38% of PV and 30% of ET patients respectively. More recent studies, however, suggest a thrombosis incidence at diagnosis of slightly less than 10% in both PV and ET patients. Arterial thrombosis comprised 60-80% of these events; microvascular disturbances occurred in over 20% of patients with either PV or ET, while hemorrhage occurred in less than 10%. Studies to determine the pathophysiology of thrombosis in PV

and ET have indicated that age greater than 65 years and a prior thrombosis are major risk factors for thrombosis in PV, and most recently, a leukocyte count greater than $15 \times 10^9/\text{mL}$ has been suggested as an additional risk factor for myocardial infarction but not other cardiovascular events. For ET, age greater than 65 years, a prior thrombotic event and cardiovascular co-morbidities have been identified as predictive of recurrent thrombotic events. Most recently, a leukocyte count of at least $8.7 \times 10^9/\text{mL}$ at diagnosis was observed to be associated with increased thrombotic risk in otherwise low risk ET patients. In general, recurrent thromboses tended to occur in the same vascular anatomy, arterial or venous, as the index one. Importantly, the platelet count has not been proved to be a thrombotic risk factor in either ET or PV, although a high platelet count is associated with bleeding in both disorders. Expression of JAK2 V617F has also not been correlated with thrombotic risk in most studies of PV or ET, with the exception of intra-abdominal venous thrombosis. With respect to proposed risk factors, in no controlled, prospective, clinical trial of either ET or PV to date has leukocyte or platelet count reduction with hydroxyurea prevented either venous or arterial thrombosis compared with nonmutagenic agents. Hydroxyurea was, however, effective in alleviating transient ischemic attacks, presumably because it is a nitric oxide donor. In PV, the most effective method for preventing thrombotic events is still phlebotomy to a hematocrit less than 42% in a woman and less than 45% in a man.

S3B-3. Overcoming blast crisis in chronic myeloid leukaemia – have we been successful?

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Abstract not available at time of printing.