THALIDOMID IN IDIOPATHIC MYELOFIBROSIS

A STATUS REPORT

Hans C. Hasselbalch¹ & Eva Lengfelder²

Department of Hematology X¹
Odense University Hospital, Odense Denmark

Department of Medicine ²
Mannheim University Hospital, Mannheim Germany.
December 19, 2004

Introduction

Idiopathic myelofibrosis is characterized by progressive accumulation of connective tissue in the bone marrow which is accompanied by extramedullary haematopoiesis with enlargement of the spleen and liver (1-8). The clinical course is chronic in the large majority of patients, although a subgroup is characterised by a rapidly lethal course with death within a few months from diagnosis (acute myelofibrosis) (5,8,9). In recent years it has become clear that the classical clinical phenotype of IMF as described above is preceded by a prefibrotic stage, which clinically may mimic essential thrombocytosis (10,11). Besides bone marrow fibrosis IMF is featured by a marked angiogenesis in the bone marrow and spleen. Indeed, neovascularisation of the bone marrow has been described many years ago as highly characteristic of idiopathic myelofibrosis (12,13) being most pronounced in patients with osteomyelosclerosis but present in the other chronic myeloproliferative disorders as well (12-19). These stromal changes are considered to develop consequent to the release of various growth factors from rapidly proliferating, large and dysplastic megakaryocytes always located in clusters near to sinusoids (20-28). These growth factors include among others platelet-derived growth (PDGF), basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and transforming growth factor beta (TGF-beta), which are mitogenic for fibroblast and/or endothelial proliferation. Concerning VEGF elevated levels of this growth have also been found in a high proportion of patients with IMF (29-32).

The treatment of idiopathic myelofibrosis aims at reducing the hypermetabolic symptoms associated with clonal myeloproliferation/myeloaccumulation and myeloid metaplasia (1-3,5,7). Conventionally these patients have been treated with busulphan or hydroxyurea. Both drugs are potentially leukemogenic – at least when being used sequentially in this patient group (33). In younger patients alpha-interferon or PEG-Intron may be useful alternatives (34,35). Besides treatment with iron, folic acid and vitamin B12, anemia in IMF may be corrected by treatment with recombinant human erythropoetin, danazol or prednisolone (2,3,5,36-38). In recent years several novel treatment modalities have been tried (38,39). Considering the pronounced angiogenesis in the bone marrow and spleen and the potential pathogenetic role of VEGF treatment with thalidomide – either as monotherapy or as combinational therapy with prednisolone – has been used in these patients (40-55). Low-dose Thalidomide + prednisolone appears to be highly successful in correcting anemia with a response rate of about 50-60%. However, in only a subgroup of patients a regression of spleen size is recorded. As one of the deliverables in WP9. CMPD this report
summarizes the results obtained in clinical trials on thalidomide in IMF, and presents proposals for future trials with thalidomide/thalidomide analoges in combination with other agents based upon their potential mechanisms of action.

**Studies on Thalidomide in Idiopathic Myelofibrosis**

Several studies dealing with the efficacy and safety of thalidomide in IMF have shown that some patients benefit from treatment with thalidomide as evidenced by an increase in the Hb-concentration and a decrease in spleen size (40-55). The treatment is very often associated with significant side effects in particular when using doses above 100-200 mg, whereas low-dose thalidomide (50mg/day) in combination with prednisolone seems to be associated with far less side effects but still highly effective with an increase in the HB-concentration in about 60% of the patients (48,53). However, there is still a need to minimize non-haematologic toxicity associated with thalidomide therapy. In this context the novel thalidomide analoges seem very promising (56-58).

**Thalidomide Analoges**

**CC-5013 (Lenalidomide; Revlimid)** is an immunomodulatory analog of thalidomide that is substantially more potent than the parent drug in terms of both anti-angiogenic and anti-TNF-alpha activity. The compound has also significantly fewer non-haematologic toxicities and has shown very promising results in both multiple myeloma (59,60), the myelodysplastic syndrome (61) as well as in idiopathic myelofibrosis (62).

**Discussion and Conclusion:** Bases upon the very promising results from studies on low-dose thalidomide and prednisolone in IMF a randomised study of a large series of patients is needed to clarify if combinational therapy with Revlimid + glucocorticoids are superior to Revlimid and glucocorticoid monotherapy (dexamethasone (Dex) (40 mg daily on days 1-4 and days 14-17 every month for six months). Combinational therapy with other novel potent antiangiogenic agents (eg. Bevacizumab (63-66), bortezomib (67-76), arsenic trioxide (77-80), histone deacetylase inhibitors (81-87), PTK787 (88-93), zoledronic acid (94-97) is relevant to consider in ensuing studies to target simultaneously multiple aberrant signal transduction pathways responsible for the enhanced myeloproliferation, decreased apoptosis (myeloaccumulation) and the marked endothelial proliferation in idiopathic myelofibrosis.
References

6. Ward HP & Block MH. The natural history of agnogenic myeloid metaplasia (AMM) and a critical evaluation of its relationship with the myeloproliferative syndrome. Medicine (Baltimore) 1971; 50: 357.


93. List AF, Giles F, Rae PE, Dugan M, Greenberg J, Osama S, Schuster MW, Laurent D, Feldman EJ. Phase I trial of PTK787/ZK 222584, an inhibitor of vascular endothelial growth factor receptor tyrosine kinases, in acute myeloid leukaemia and myelodysplastic syndrome. Blood 2002; 100(11); abstract # 13 08.