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EDITORIAL

Treatment considerations for primary myelofibrosis

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Primary myelofibrosis (PMF) belongs to the group of Philadelphia chromosome negative (Ph^-) chronic myeloproliferative neoplasms caused by a clonal stem cell disorder presenting with myeloproliferation and fibrosis. The clinical presentation is characterised by anaemia, marked hepatosplenomegaly, leuko-erythroblastosis, constitutional symptoms and finally leukaemic transformation. Myelofibrosis may also develop as a secondary complication of two other myeloproliferative neoplasms, essential thrombocytosis (ET) and polycythemia vera (PV).

The median survival of patients with MF is less than five years; this is, however, strongly dependent on risk factors that have been included in several prognostic scoring systems. The International Prognostic Scoring System (IPSS) for PMF uses five risk factors consisting of age (>65 years), anaemia (Hb <10 g/l), leucocyte count (>25 x 10^9/l), circulating blasts (>1%) and the presence of constitutional symptoms to categorise patients in either a high (≥3 risk factors), intermediate-high (2 risk factors), intermediate-low (1 risk factor) or low (no risk factors) risk group with a median survival of 27, 48, 95, or 135 months, respectively. Besides these risk factors the prognosis of patients with MF is also strongly dependent on the presence of cytogenetic abnormalities, transfusion dependency and the presence of comorbidity. The pathophysiology of MF is not fully elucidated but is characterised by a disturbed bone marrow physiology with expression of multiple growth factors, the release of cytokines, enhanced neoangiogenesis and profound fibrosis in which megakaryocytes, monocytes and clonal stem cells play an important role.[1]

Traditionally, patients with MF are treated with supportive care to reduce anaemia, generally by transfusion and the administration of prednisone, danazol or erythropoietin. Splenectomy, splenic radiation or administration of hydroxyurea has been used to treat the often massive splenomegaly in patients with MF. Although sometimes helpful, these palliative treatments usually only have a limited effect on the clinical presentation with a relatively short duration. The only curative option in patients with MF is allogeneic stem cell transplantation, which has been demonstrated to result in five-year survival rates of up to 50 to 65% depending on the age, risk factors and comorbidity of the patient. Allogeneic stem cell transplantation is, however, frequently complicated by unacceptable treatment-related mortality (up to 30%) and morbidity in the form of graft versus host disease and graft rejection, which seems to be more frequent in patients with MF than allogeneic stem cell transplantation in other haematological malignancies. Furthermore, the median age patients are diagnosed with MF is 67 years, which limits the possibility to use allogeneic stem cell transplantation as a curative option in a substantial number of the patients.[2]

New therapeutic options represent forms of targeted therapy aiming at the disturbed physiology of the bone marrow in these patients. One of such therapies is the immune-modulating drugs (IMIDs) such as thalidomide and lenalidomide, which act by downregulating the pro-inflammatory response and inhibition of neo-angiogenesis, which have been in particular successful in the treatment of multiple myeloma. In this issue of the Netherlands Journal of Medicine, Holle *et al.* compare the efficacy of both drugs in patients with PMF.[3] The data consist of a retrospective analysis of patients with PMF treated with thalidomide or lenalidomide in two hospitals in the Netherlands. In line with previous observations the authors have shown that treatment with thalidomide induces a clinical response in almost half of the patients but appears to be poorly tolerated due to side effects such as neuropathy and constipation. As discussed by the authors, others found this regime to be more tolerable in combination with prednisone.[4,5] Lenalidomide, which is characterised by a more potent immune-modulating effect than thalidomide and is better tolerated, also proved to produce a clinical response in half of the patients in the study by Holle *et al.* similar to previous observations by others.[6,7] Interestingly, a new IMID, pomalidomide, either alone or in combination with prednisone, was

recently demonstrated to be effective in reducing anaemia in patients with PMF without serious side effects such as neuropathy or severe myelosuppression.[8]

Besides these immune-modulating drugs other forms of target therapy have been studied in MF. Following the successful introduction of epigenetic therapy in the treatment of myelodysplastic syndrome and acute myeloid leukaemia, hypomethylating agents, such as 5-azacitidine, and histone deacetylase inhibitors, have been demonstrated to be effective in MF and are currently being evaluated in clinical trials.[9,10] Finally, much research is aimed at the JAK2 pathway since half of the patients with MF appear to have the JAK2V167F mutation, which is also found in 50% of the patients with ET and in almost all patients with PV. JAK2 inhibitors are currently being tested in patients with MF and in small studies JAK2 inhibition appeared to reduce splenomegaly and constitutional symptoms but seems to be less effective in reducing anaemia and transfusion dependency.[11]

In conclusion, multiple therapeutic options will soon become available for the treatment of MF patients when allogeneic stem cell transplantation is not feasible. Given the results presented and discussed by Holle *et al.* and the extensive experience with these agents in the treatment of multiple myeloma, treatment with thalidomide or lenalidomide should be considered in patients with PMF or post ET/PV MF who are not considered to be candidates for allogeneic stem cell transplantation or have no donor.

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