

Mini-dose of thalidomide for treatment of primary myelofibrosis. Report of a case with complete reversal of bone marrow fibrosis and splenomegaly

We report a patient with very advanced myelofibrosis and huge splenomegaly who showed a complete hematological response to low dose thalidomide with reversal of splenomegaly and bone marrow fibrosis after 30 months of the treatment

Haematologica 2007; 92(2):e15-e16

Primary myelofibrosis is a chronic progressive disorder incurable except for allo-transplantation in young patients¹. Thalidomide which down-regulates cytokine release involved in fibrosis and angiogenesis (VEGF, TGF-beta, beta-FGF, PDGF), has been used with variable responses in the treatment of MF²⁻⁶. Thalidomide induced improvement in disease-associated anemia and thrombocytopenia and in some cases decreased splenomegaly. We report here a patient who achieved a complete response of MF, including complete reversal of splenomegaly and bone marrow fibrosis, after being treated with low doses thalidomide. A 82-year-old patient, with no other medical problems, was followed since 1993 because of erythrocytosis and mild splenomegaly. His bone marrow biopsy revealed myeloid tree-lineage hyperplasia and moderate fibrosis. The patient was initially treated with phlebotomy when needed, and afterwards by a low dose of hydroxyurea. Five years later, when anemia developed (Hb <10 g/L), together with prominent splenomegaly (18 cm) and aggravation of bone marrow fibrosis, combination treatment with androgen fluoxymesterone, vitamin B1, B6 and B12 complex and folic acid was started. The anemia was temporarily stabilized; however, since 2003 the patient became transfusion dependent (2 packed red cell every 3 weeks). At that time, he had a huge splenomegaly up to pubis, Hb 8.3 g/dl, WBC $4 \times 10^9/L$, Plt $75 \times 10^9/L$ and LDH 1220 U. His peripheral blood smear showed tear drop cells, normoblasts and occasionally blasts. Bone marrow biopsy revealed severe reticulin and collagen fibrosis with no hematopoiesis (Figure 1). In view of the progressive painful splenomegaly and deep pancytopenia, splenectomy was advised but refused by the patient.

Therefore alternative treatment with thalidomide was considered and started at a dose of 50 mg/day together with prednisone 5 mg/day in March, 2004. B-complex and folic acid were continued. Four months later, the blood transfusion requirement decreased and gradually was abolished. The spleen size started to be smaller and became impalpable. Currently, after 30 months of treatment, the blood count showed Hb 12.0 g/dL, WBC $2.6 \times 10^9/L$, Plt $140 \times 10^9/L$. The repeated bone biopsy showed a dramatic change with complete normalization of hematopoiesis and total resolution of collagen. The blood film doesn't disclose any tear drops. The JAK2 (V617F) tested recently, was found as a heterozygous pattern. Based on thalidomide anti-angiogenic properties, this agent has been recently evaluated in MF. Thalidomide monotherapy in moderate and high doses (200-800 mg/day) produces a 20-50% response rate in MF-associated anemia and thrombocytopenia, had mild impact on splenomegaly, but is poorly tolerated²⁻⁶. Recently, results of the first multicenter randomized trial comparing thalidomide 400 mg/day with placebo were reported in 52 patients with anemia.⁶ This study failed to show an advantage of thalidomide. Many patients were withdrawn early from treatment because of adverse effects. The main side effects complicating the treatment were fatigue, sedation, constipation, peripheral neuropathy, tremor and rash. Mesa *et al.*³ improved tolerability and efficacy of this medication, using thalidomide in low dose 50 mg/day along with a three months oral prednisone, which began at dose 0.5 mg/kg/day with tapering off. Thalidomide was well tolerated; 20 out of 21 enrolled in this trial patients completed 3 months of therapy. An objective clinical response was demonstrated in 62% patients. Among 10 patients with severe anemia, 7 showed reduction of blood transfusion requirements or became transfusion-independent. More than 50% increase in platelet counts was seen in 6 out of 8 patients with thrombocytopenia, while in 19% of all treated patients spleen size decreased by >50%. No disappearance of collagen fibrosis in bone marrow and reversal to normal spleen size had been reported before.

In conclusion, we report a patient with a very advanced MF who showed complete hematological response to low dose thalidomide with complete reversal of bone marrow fibrosis and splenomegaly. We suggest that this exceptional response might be due to the long tolerable continuous treatment and a combination with prednisone, B-complex vitamins and folic acid.

A. Berrebi,^{1*} E. Feldberg,² I. Spivak,³ L. Shvidel¹

¹Hematology Institute, Kaplan Medical Center, ²Rehovot, Pathology Department, Kaplan Medical Center, Rehovot, Internal Medicine Department, Yoseftal Hospital, ³Eilat, Israel

*Corresponding author: Alain Berrebi

Hematology Institute, Kaplan Medical Center, Rehovot, Israel 76100.

Tel: 972-89444383; Fax: 972-894441706;

E-mail: alain_b@clalit.org.il

Key words: myelofibrosis, thalidomide

Figure 1. Bone biopsy in primary myelofibrosis showing reversal of collagen fibrosis after low dose thalidomide (a, b - before treatment; c, d - post treatment). a, c - hematoxyline-eosine stain; b, d - Masson's trichrome stain.

References

1. efferi A. Survivorship and prognosis in myelofibrosis with myeloid metaplasia. *Leuk Lymphoma* 2006;47:379-80.
2. Merup M, Kutti J, Birgergard G, Mauritzson N, Bjorkholm M, Markevarn B, *et al.* Negligible clinical effects of thalidomide in patients with myelofibrosis with myeloid metaplasia. *Med Oncol* 2002;19:79-86.
3. Mesa RA, Steensma DP, Pardanani A, Li CY, Elliott M, Kaufmann SH, *et al.* A phase 2 trial of combination low-dose thalidomide and prednisone for the treatment of myelofibrosis with myeloid metaplasia. *Blood* 2003;101:2534-41.
4. Marchetti M, Barosi G, Balestri F, Viarengo G, Gentili S, Barulli S, *et al.* Low-dose thalidomide ameliorates cytopenias and splenomegaly in myelofibrosis with myeloid metaplasia: a phase II trial. *J Clin Oncol.* 2004; 22:424-31.
5. Thomas DA, Giles FJ, Albitar M, Cortes JE, Verstovsek S, Faderl S, *et al.* Thalidomide therapy for myelofibrosis with myeloid metaplasia. *Cancer* 2006;106:1974-84.
6. Abgrall JF, Guibaud I, Bastie JN, Flesch M, Rossi JF, Lacotte-Thierry L, *et al.* Thalidomide versus placebo in myeloid metaplasia with myelofibrosis: a prospective, randomized, double-blind, multicenter study. *Haematologica* 2006;91:1027-32.