

### Thalidomide therapy in compensated and decompensated myelofibrosis with myeloid metaplasia

Six patients affected by myelofibrosis were treated with increasing doses of thalidomide. Three of them showed a good response, while the patients with advanced disease did not respond. A decrease of bone marrow angiogenesis was noted in the responders. This study confirms some preliminary reports showing that thalidomide could play a role in the treatment of the early phases of myelofibrosis.

Myelofibrosis with myeloid metaplasia is a rare<sup>1</sup> myeloproliferative disorder characterized by bone marrow fibrosis and extramedullary hematopoiesis. Increased levels of extra cellular matrix and angiogenesis have recently been reported in this disease.<sup>2</sup> These changes seem to be secondary to excessive production of several cytokines such as vascular endothelial growth factor, transforming growth factor  $\beta$ , and basic fibroblastic growth factor.<sup>3,4</sup>

The conventional therapy for myelofibrosis is largely palliative, and no conventional drug has been shown to improve the patients' survival. Recently, new drugs targeting the megakaryocyte-cytokine-fibroblast axis, e.g. anagrelide, suramin and pirlfenidone, have been used.<sup>5,6</sup> The increased bone marrow angiogenesis has suggested that anti-angiogenesis agents could be useful in this disease. Thalidomide, the most popular and cheapest anti-angiogenesis drug,<sup>7</sup> could be particularly useful since it is also endowed with strong anti-cytokine properties. In addition, one preliminary report indicated that this drug has therapeutic activity in myelofibrosis.<sup>8</sup> On the basis of these findings, we have started a study to assess the efficacy and tolerability of thalidomide in myelofibrosis in patients with any stage of the disease.

Between January and February 2000, we enrolled 6 patients with myelofibrosis. In all cases the diagnosis was made by standard criteria; bcr-abl rearrangement (determined by polymerase chain reaction) was negative in all patients. Three patients had stable disease, without requiring transfusions (compensated myelofibrosis), while the others had become transfusion-dependent, requiring from 2 to 4 packed red blood cell units per month (decompensated myelofibrosis).

Before starting therapy each patient underwent bone marrow biopsy and spleen measurement by ultrasonography. Bone marrow biopsy was repeated every six months and ultrasonography every month. Thalidomide was administered orally (100 mg tablet) starting with a dose of 100 mg/daily which was gradually increased to the maximum dose tolerated. All patients gave informed consent to the study and treatment.

The effects of the therapy on hemoglobin level and spleen size are shown in Figure 1. As shown, no effects on hemoglobin level, leukocyte count, or spleen size were observed in patients with decompensated myelofibrosis. In contrast, in compensated patients the mean hemoglobin level increased, the spleen size decreased, and leukocyte count returned to a normal level. The main side effects of the therapy were asthenia (100%), fluid retention (75%), and constipation (50%).

The treatment did not change the bone marrow morphology in non-responders, while a reduction of bone marrow cellularity was shown in the responders. In these cases, the marrow angiogenesis, evaluated as microvascular density, was reduced, but not statistically significant so (from 6.0 to 4.5). To explain this partial result, the short observation period, the long life of endothelial cells, and the low number of cases should be taken in account.

On the basis of these preliminary results, thalidomide seems to have some therapeutic activity in myelofibrosis. The drug does not seem to be useful in the advanced stages of the disease, when extreme fibrosis or osteosclerosis have developed, where-

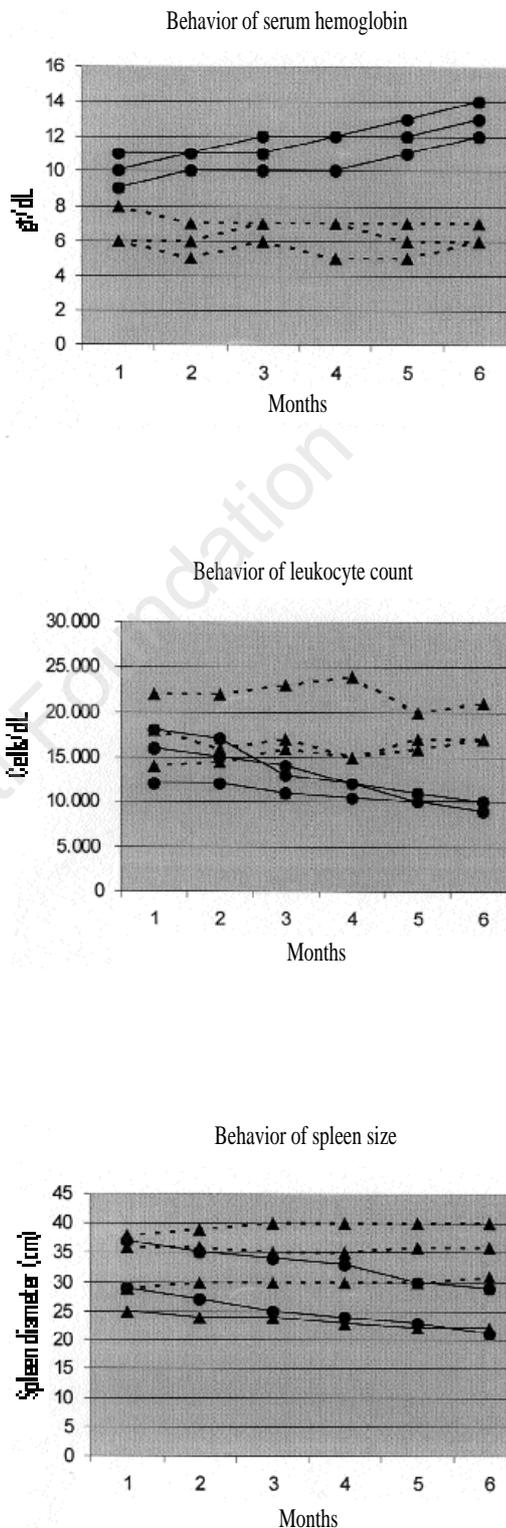


Figure 1. K Compensated myelofibrosis. G Decompensated myelofibrosis.

as it does seem to have a good efficacy in compensated myelofibrosis improving hemoglobin levels and reducing the size of the spleen. Despite some discouraging results,<sup>9</sup> the drug merits further clinical trials.

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