is thalidomide a true anti-angiogenic molecule in multiple myeloma?

In the March issue of this journal Patrizia Tosi and Michele Cavo reported about the use of thalidomide in multiple myeloma (MM).1 They underline that the mechanisms of action of thalidomide are poorly defined yet. Among them (some of which are only hypothesized2), one of the most controversial is whether thalidomide acts as an anti-angiogenic.

The use of thalidomide in patients with end-stage refractory MM proposed by Singhal et al.,3 was based on our observations,4-6 showing an increased bone marrow microvascularity in MM, and those7-9 showing that thalidomide is apoptogenic for neovascularisation and inhibits angiogenesis in several experimental models. In 1994, D’Amato et al.7 demonstrated that thalidomide inhibits fibroblast growth factor-2 (FGF-2)-induced angiogenesis in a rabbit cornea micropocket assay. Later, he reported that thalidomide also inhibits vascular endothelial growth factor (VEGF) in a murine model of corneal vascularization,8 and others demonstrated that thalidomide inhibits microvesSEL formation in a rat aorta ring assay.9

As far as concerns MM treatment, no close relationship between microvesSEL density and clinical response was found in the study by Singhal et al.10-13 In contrast, its efficacy in acquired immunodeficiency syndrome (AIDS)-related Kaposis’s sarcoma is striking.4-14

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According to its anti-angiogenic power, thalidomide has been used in solid tumors, such as recurrent glioma, breast cancer, melanoma, renal and ovarian cancer and hormone-refractory prostate cancer, producing, however, limited therapeutic activity.10-13 In contrast, its efficacy in acquired immunodeficiency syndrome (AIDS)-related Kaposis’s sarcoma is striking.4-14

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References

Inside Haematologica: caution in the use of thalidomide for treatment of hematologic disorders

In this issue of Haematologica, Tosi et al. report further data on the potential usefulness of thalidomide in the treatment of patients with multiple myeloma. From October 1999 to January 2001, 65 patients with relapsed/refractory myeloma were treated with thalidomide. Sixty patients are presently evaluable for response; of these, 17 (28.3%) showed ≥ 25% tumor reduction, for a total response rate averaging 46.6%. These data confirm that thalidomide is active in patients with advanced relapsed/refractory multiple myeloma and represent the basis for ongoing clinical trials aimed at testing the role of this drug as front line therapy for newly diagnosed disease. Several papers on the use of thalidomide have appeared in this journal in the last months.2-9 Two other papers specifically addressed the issue of complications of thalidomide therapy.10,11 In particular, Camba et al.10 have reported on 5 patients who developed deep vein thrombosis of the lower limbs while on thalidomide and chemotherapy. In a larger study, Zangari et al.12 observed the occurrence of deep vein thrombosis (DVT) in 14 of 50 patients (28%) randomly assigned to receive thalidomide but in only 2 of 50 patients (4%) not given the agent. Anticoagulation was effective and thalidomide was resumed safely in 75% of patients. Zangari et al.12 conclude that thalidomide given in combination with multiagent chemotherapy and dexamethasone is associated with a significantly increased risk of DVT, which appears to be safely treated with anticoagulation and does not necessarily warrant discontinuation of thalidomide.

The above reports have important clinical implications. Since the use of thalidomide in the treatment of multiple myeloma is expanding, clinicians should be aware of the risk of DVT. The presence of additional risk factors13,14 should likely be taken into account and close monitoring should be performed facing a patient with a potential complication.15,16

Since several hematologic disorders are refractory to therapy, there is a tendency to use any new drug, or newly used agent in their treatment. Thus, thalidomide has already been used in patients myelofibrosis with myeloid metaplasia17,19 or in patients with myelodysplastic syndrome.20,21 There is no evidence that thalidomide is useful for patients with myelofibrosis with myeloid metaplasia whereas it is clear that it has major adverse effects that may include DVT. As usual, phase I/II trials in MDS patients22 appear to be promising with a subset of patients showing a definite response to thalidomide. In the last fifteen years this has already been found with dozens of agents that are no longer employed nowadays. In conclusion, patients with multiple myeloma may benefit from thalidomide, but this drug should administered with caution, paying attention, in particular, to the risk of deep vein thrombosis. On