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 hypothesized[2]), 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 those[7-9] showing that thalidomide is apoptogenic for neovasculature 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]

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 Kaposi's sarcoma is striking.[14]

As far as concerns MM treatment, no close relationship between microvessel density and clinical response was found in the study by Singhal *et al.*:[3] there is no difference in the bone marrow microvascular density between responsive and resistant patients. However, the lack of significant lowering in bone marrow microvascular density after thalidomide therapy, does not fully rule out the anti-angiogenic mechanism of action of the drug. Now, Cheng *et al.*[15] suggest a relationship between bone marrow microvascularity and clinical response to thalidomide, since they demonstrated that an increased pretreatment microvascular density could predict the response. Moreover, while Rajkumar *et al.*[16] demonstrated that VEGF secretion by MM cell lines is not influenced by *in vitro* treatment with thalidomide, Weber *et al.*[17] showed that VEGF serum levels are high in responding patients.

While angiogenesis inhibition remains an attractive potential mechanism of action, thalidomide has a number of other properties that could explain its activity in MM. These include disturbance of adhesion molecule expression that prevents myeloma cell interaction with bone marrow microenvironment,[18] modulation of tumor necrosis factor-α production by stimulated monocytes, macrophages and neutrophils,[19] and enhancement of cell-mediated immunity by direct co-stimulation of T-cells.[20]

To sum up, because a causal relationship between the anti-angiogenic effect of thalidomide and clinical activity against neoplastic diseases has still to be demonstrated, it is conceivable to hypothesize that multiple pathways may be involved in thalidomide acitivity in MM. Moreover, the rapid response usually observed is consistent with either a direct cytotoxic effect or an immunomodulatory effect. Further studies are warranted to establish possible correlations between elevated blood levels of VEGF and FGF-2, bone marrow angiogenesis and the likelihood of response.

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References

1. Tosi P, Cavo M. Thalidomide in multiple myeloma: state of art. Haematologica 2002; 87:233-4.
2. Richardson P, Hideshima T, Anderson K. Thalidomide: emerging role in cancer medicine. Ann Rev Med 2002; 53:629-57.
3. Singhal S, Mehta J, Desikan R, Ayers D, Roberson P, Eddlemon P, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999; 341: 1565-71.
4. Vacca A, Ribatti D, Roncali L, Ranieri G, Serio G, Silvestris F, et al. Bone marrow angiogenesis and progression in multiple myeloma. Br J Haematol 1994; 87:503-8.
5. Vacca A, Di Loreto M, Ribatti D, Di Stefano R, Gadaleta-Caldarola G, Iodice G, et al. The bone marrow of patients with active multiple myeloma: angiogenesis and plasma cell adhesion molecules LFA-1, VLA-4, LAM-1 and CD-44. Am J Hematol 1995; 50:9-14.
6. Vacca A, Ribatti D, Presta M, Minischetti M, Iurlaro M, Ria R, et al. Bone marrow neovascularization, plasma cell angiogenic potential, and matrix metalloproteinase-2 secretion parallel progression of human multiple myeloma. Blood 1999; 93:3064-73.
7. D'Amato RJ, Laughnan ES, Flynn E, Folkman J. Thalidomide is an inhibitor of angiogenesis. Proc Natl Acad Sci USA 1994; 91:4082-5.
8. Kenyon BM, Browne F, D'Amato RJ. Effects of thalidomide and related metabolities in a mouse corneal model of neovascularization. Exp Eye Res 1997; 64:971-8.

9. Raver KS, Dixon SC, Figg WD. Inhibition of angiogenesis by thalidomide requires metabolic activation, which is species dependent. Biochem Pharmacol 1998; 55: 1827-34.
10. Fine HA, Figg WD, Jaeckle K, Wen PY, Kyritsis AP, Loeffler JS, et al. Phase II trial of the antiangiogenic agent thalidomide in patients with recurrent high grade gliomas. J Clin Oncol 2000; 18:708-15.
11. Baidas SM, Winer EP, Fleming GF, Harris L, Pluda JM, Crawford JG, et al. Phase II evaluation of thalidomide in patients with metastatic breast cancer. J Clin Oncol 2000; 18:2710-7.
12. Eisen T, Boshoff C, Mak I, Sapunar F, Vaughan MM, Pyle L, et al. Continuous low dose thalidomide: phase II study in advanced melanoma, renal cell, ovarian and breast cancer. Br J Cancer 2000; 82: 812-7.
13. Figg WD, Raje S, Bauer KS, Tompkins A, Venzon D, Bergan R, et al. Pharmacokinetics of thalidomide in an elderly prostate cancer population. J Pharmacol Sci 1999; 88: 121-5.
14. Little RF, Wyvill KM, Pluda JM, Welles L, Marshall V, Figg WD, et al. Activity of thalidomide in AIDS-related Kaposi's sarcoma. J Clin Oncol 2000; 18: 2593-602.
15. Cheng D, Kini AR, Rodriguez J, Burt R, Pereson LC, Traynor AE. Microvascular density and cytotoxic T cell activation correlate with response to thalidomide in multiple myeloma patients. Blood 1999; 94(suppl. 1):317a.
16. Rajkumar SV, Timm M, Mesa RA et al. Effect of thalidomide on myeloma cell apoptosis and VEGF secretion. Blood 2000; 96 (suppl. 1):364a.
17. Weber DM, Rankin K, Gavino M, et al., Angiogenesis factors and sensitivity to thalidomide in previously untreated multiple myeloma. Blood 2000; 96(suppl. 1):168a.
18. Geitz H, Handt S, Zwingenberger K. Thalidomide selectively modulates the density of cell surface molecules involved in the adhesion cascade. Immunopharmacology 1996; 31:213-21.
19. Sampaio EP, Sarno EN, Galilly R, Cohn ZA, Kaplan G. Thalidomide selectively inhibits tumor necrosis factor α production by stimulated human monocytes. J Exp Med 1991; 173:699-703.
20. McHugh SM, Rifkin IR, Deighton J, Wilson AB, Lachmann PJ, Lockwood CM, et al. The immunosuppressive drug thalidomide induces T helper cell type 2 (Th 2) and concomitantly inhibits TH1 cytokine production in mitogen – and antigen – stimulated human peripheral blood mononuclear cell cultures. Clin Exp Immunol 1995; 99: 160-7.

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

In this issue of Haematologica, Tosi *et al.*[1] 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 occurence 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 factors[13,14] 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 metaplasia[17-19] 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 patients[22] 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