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

the other hand, it is very unlikely that the majority of patients myelofibrosis with myeloid metaplasia or with myelodysplastic syndrome will benefit from this agent. Any use of thalidomide for these latter unlicensed indications should take place within clinical trials.

References

1. Tosi P, Zamagni E, Cellini C, Ronconi S, Patriarca F, Ballerini F, et al. Salvage therapy with thalidomide in patients with advanced relapsed/refractory multiple myeloma. Haematologica 2002; 87:409-15.
2. Pini M, Baraldi A, Pietrasanta D, Allione B, Depaoli L, Salvi F, Levis A. Low-dose of thalidomide in the treatment of refractory myeloma. Haematologica 2000; 85:1111-2.
3. Palumbo A, Giaccone L, Bertola A, Pregno P, Bringhen S, Rus C, et al. Low-dose thalidomide plus dexamethasone is an effective salvage therapy for advanced myeloma. Haematologica 2001; 86:399-403.
4. Hus M, Dmoszynska A, Soroka-Wojtaszko M, Jawniak D, Legiec W, Ciepnuch H, et al. Thalidomide treatment of resistant or relapsed multiple myeloma patients. Haematologica 2001; 86:404-8.
5. Tosi P, Ronconi S, Zamagni E, Cellini C, Grafone T, Cangini D, et al. Salvage therapy with thalidomide in multiple myeloma patients relapsing after autologous peripheral blood stem cell transplantation. Haematologica 2001; 86:409-13.
6. Zappasodi P, Lorenzi A, Corso A. The irreplaceable image. Thalidomide in refractory myeloma patients: early changes in bone marrow cellularity. Haematologica 2001; 86:448.
7. Pozzato G, Zorat F, Nascimben F, Comar C, Kikic F, Festini G. Thalidomide therapy in compensated and decompensated myelofibrosis with myeloid metaplasia. Haematologica 2001; 86:772-3.
8. Tosi P, Cavo M. Thalidomide in multiple myeloma: state of art. Haematologica 2002; 87:233-4.
9. Corso A, Lorenzi A, Orlandi E, Astori C, Mangiacavalli S, Lazzarino M. Advantages of using thalidomide for the management of refractory myeloma patients. Haematologica 2002; 87:327-8.
10. Camba L, Peccatori J, Pescarollo A, Tresoldi M, Corradini P, Bregni M. Thalidomide and thrombosis in patients with multiple myeloma. Haematologica 2001; 86:1108-9.
11. Pitini V, Arrigo C, Aloi G, Azzarello D, La Gattuta G. Diabetic foot disease in a patient with multiple myeloma receiving thalidomide. Haematologica 2002; 87:ELT07.
12. Zangari M, Anaissie E, Barlogie B, Badros A, Desikan R, Gopal AV, et al. Increased risk of deep-vein thrombosis in patients with multiple myeloma receiving thalidomide and chemotherapy. Blood 2001; 98:1614-5.
13. Aznar J, Vaya A, Estelles A, Mira Y, Segui R, Villa P, et al. Risk of venous thrombosis in carriers of the prothrombin G20210A variant and factor V Leiden and their interaction with oral contraceptives. Haematologica 2000; 85:1271-6.
14. Margaglione M, Brancaccio V, Ciampa A, Papa ML, Grandone E, Di Minno G. Inherited thrombophilic risk factors in a large cohort of individuals referred to Italian thrombophilia centers: distinct roles in different clinical settings. Haematologica 2001; 86:634-9.
15. Villa P, Ferrando F, Serra J, Faus H, Mira Y, Vaya A, et al. Quantification of D-dimer using a new fully automated assay: its application for the diagnosis of deep vein thrombosis. Haematologica 2000; 85:520-4.
16. Siragusa S, Terulla V, Pirrelli S, Porta C, Falaschi F, Anastasio R, et al. A rapid D-dimer assay in patients presenting at the emergency room with suspected acute venous thrombosis: accuracy and relation to clinical variables. Haematologica 2001; 86:856-61.
17. Tefferi A, Elliot MA. Serious myeloproliferative reactions associated with the use of thalidomide in myelofibrosis with myeloid metaplasia. Blood 2000; 96:4007.
18. Barosi G, Grossi A, Comotti B, Musto P, Gamba G, Marchetti M. Safety and efficacy of thalidomide in patients with myelofibrosis with myeloid metaplasia. Br J Haematol 2001;114:78-83.
19. Canepa L, Ballerini F, Varaldo R, Quintino S, Reni L, Clavio M, et al. Thalidomide in agnogenic and secondary myelofibrosis. Br J Haematol 2001; 115:313-5.
20. Strupp C, Germing U, Aivado M, Misgeld E, Haas R, Gattermann N. Thalidomide for the treatment of patients with myelodysplastic syndromes. Leukemia 2002;16:1-6.
21. Zorat F, Shetty V, Dutt D, Lisak L, Nascimben F, Allampallam K. The clinical and biological effects of thalidomide in patients with myelodysplastic syndromes. Br J Haematol 2001;115:881-94.
22. Alessandrino EP, Amadori S, Cazzola M, Locatelli F, Mecucci C, Morra E, et al. Myelodysplastic syndromes: recent advances. Haematologica 2001; 86:1124-57.