Thalidomide analogs

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Thalidomide-based regimens have shown remarkable activity in relapsed-refractory multiple myeloma (MM) so that their use has been successfully extended to newly diagnosed patients. Thalidomide-dexamethasone combination has demonstrated to be superior to VAD in terms of both response rate and relative reduction of serum or urine M component,[1] and these results are being confirmed in multicenter randomised ongoing trials.[2] A major drawback of thalidomide is represented by its side effects; more than half of the patients complain about lethargy and constipation, deep venous thromboses occur in up to 15-20% of newly diagnosed patients treated with thalidomide-dexamethasone unless a proper prophylaxis is performed[3-4] grade ≥2 WHO peripheral neuropathy is reported in 60% of the patients treated longer than 1 year;[5] the incidence and extent of side effects limit the usage of thalidomide in other hematological conditions such as Waldenstrom macroglobulinemia, AL amyloidosis and, above all, myelofibrosis.[6-7] Thalidomide analogs were synthesized in order to obtain compounds displaying an antineoplastic activity comparable or superior to that of thalidomide, with fewer side effects. The mechanism of action of thalidomide has not been fully elucidated yet. Although this compound is a potent inhibitor of angiogenesis, its activity in MM and other hematological disorders is more likely to be due to its interaction with bone marrow stromal cells and to the subsequent inhibition of the secretion of TNF-α and IL-6 and to the downregulation of adhesion molecules.[8] Furthermore, thalidomide modulates the immune system promoting the growth of NK and T lymphocytes and increasing the production of IL-2 and γ-IFN.[9] Thalidomide analogs were initially selected basing on their ability of inhibiting TNF-α. Two classes of drugs were made available: selected cytokine inhibitors (SelCID) that inhibit phosphodiesterase 4 production and angiogenesis, and immunomodulatory drugs (IMIDs).[10] This latter class of thalidomide analogs stimulates the production of anti CD3-stimulated T lymphocytes resulting in a greater increase of IL2 and γ-IFN than thalidomide. IMIDs have shown to inhibit MM cell growth *in vitro*, promoting apoptosis through activation of caspase 8, and to possess a synergistic activity in combination with dexamethasone, melphalan and doxorubicin.[11] IMIDs were also more active than thalidomide *in vivo*, in suppressing the growth of MM tumors in nude mice.[12] Following these pre-clinical results, IMIDs have also been tested in clinical trials.

Actimid (CC4047) is a potent inhibitor of TNF-α (5000 fold more than thalidomide); in a phase I trial performed in 24 patients with advanced, relapsed or refractory MM, a ≥PR was obtained in 50% of the cases. Safety profile was good, maximum tolerated dose was 2 mg/day with neutropenia being the dose limiting effect; therapy-related deep venous thrombosis, however, occurred in 3 patients.[13]

Lenalidomide (Revlimid, CC5013) is at present the most widely tested thalidomide analog. The first dose-escalation phase I study was performed in 27 patients with advanced, relapsed or refractory MM.[14] A≥25% reduction in paraprotein was obtained in 17 out of 24 evaluable patients (71%); no significant lethargy, constipation or neuropathy were observed at any dose level, however, all the patients treated with lenalidomide 50 mg/day experienced grade 3 myelosuppression, so that 25 mg/day was considered as the maximum tolerated dose. A similar study was performed in 15 patients who had relapsed after high-dose therapy[15] a ≥PR was obtained in 20% of the cases. Following these results, two phase II studies were designed. The first one aimed at evaluating the efficacy and the toxicity of lenalidomide 15 mg BID vs. 30 mg/day, and an increased incidence of cytopenia was observed in the first group.[16] A second phase II study was designed in order to assess the efficacy and safety of single agent lenalidomide at 30 mg/day for 21 days every 28 days in relapsed/refractory MM.[17] Two hundred and twenty-two patients were enrolled; a ≥25% paraprotein reduction was observed in 28% of the cases. Impor-

tantly, the incidence of neuropathy was markedly reduced as compared to what has been described in thalidomide-treated patients; the most commonly reported adverse events were neutropenia (38%) and thrombocytopenia (22%). A subsequent randomised, double blind phase III study was performed in order to evaluate the efficacy and the safety of intermittent 25 mg/day lenalidomide (on days 1-21 of a 28 days cycle) plus high-dose dexamethasone vs. placebo plus high-dose dexamethasone in relapsed/refractory MM.[18] Three hundred fifty-four patients were enrolled in USA and Europe, in the lenalidomide-dexamethasone group response rate (CR + PR) approached 50% (vs. 20% in the placebo-dexamethasone group), and median TTP has not been reached at 15 months. Grade 4 hematological toxicity was recorded in 10-15% of the cases, while less than 10% of the patients complained about neurotoxicity, fatigue or constipation. Lenalidomide plus dexamethasone was also tested in a prospective, phase III trial in 30 newly diagnosed MM patients, and a PR was achieved in 83% of them. Lenalidomide showed a promising activity also in myelodysplastic syndrome (MDS)[19] Forty-three patients with transfusion dependent symptomatic anemia were treated with lenalidomide 25-10 mg/day for 21 days every 28-days cycle; a response was obtained in 56% of the cases, with 20/43 achieving independence from transfusion. The response rate was highest among individuals with clonal interstitial deletion of chromosome 5q31.1 (83% vs. 57% in patients with normal karyotype) and in patients with low prognostic risk. Neutropenia and thrombocytopenia were observed in > 65% of the cases and resulted in dose reduction in 58% of the patients; other adverse events were mild and infrequent. Recently, a N-substituted (CPS11) and a tetrafluorinated (CPS49) thalidomide analog have demonstrated a promising activity, as they inhibit proliferation of MM cell lines, both sensitive and resistant to conventional chemotherapy, and induce MM cell apoptosis, decrease angiogenesis and overcome protective effect of IL6, IGF-1, VEGF and co-culture with bone marrow stromal cells [20] IMIDs have thus proven to be effective in the treatment of different malignancies, especially MM and low-risk MDS, while clinical trials are undergoing in solid tumor including malignant melanoma, glioma, and prostate cancer.[21] Future development will be to further exploit the combination of these drugs with compounds acting both on neoplastic cells and on tumor microenvironment, in order to potentiate synergism and to minimize the occurrence of resistance.

References

1. Cavo M, Zamagni E, Tosi P et al. Superiorità of thalidomide and dexamethasone over vincristin-doxorubicin-dexamethasone (VAD) as primary therapy in preparation for autologous transplantation for multiple myeloma. Blood 2005;106:35-9.
2. Rajkumar SV, Blood E, Vesole DH et al. Thalidomide plus dexamethasone versus dexamethasone alone in newly diagnosed multiple myeloma: results of a phase III trial coordinated by the Eastern Cooperative Oncology Group. Blood 2004;104:63a.
3. Cavo M , Zamagni E, Cellini C et al. Deep vein thrombosis in patients with multiple myeloma receiving first-line thalidomide-dexamethasone therapy. Blood 2002;100: 2272-3.
4. Zangari M, Barlogie B, Anaissie A et al. Deep vein thrombosis in patients with multiple myeloma treated with thalidomide and chemoherapy: effects of prophylactic and therapeutic anticoagulation. Br J Haematol 2004; 126:715-21.
5. Tosi P, Zamagni E, Cellini C et al. Neurological toxicity of long-term (> 1 yr) thalidomide therapy in patients with multiple myeloma. Eur J Haematol 2005; 74:212-6.
6. Dimopoulos MA, Zomas A, Viniou NA et al. Treatment of Waldenstrom's macroglobulinemia with thalidomide. J Clin Oncol 2001;19:3596-60.
7. Barosi G, Elliott M, Canepa L et al. Thalidomide in myelofibrosis with myeloid metaplasma: a pooled analysis of individual patients data from five studies. Leuk Lymphoma 2002;43:2301-7.
8. Kumar S, Witzig TE, Rajkumar SV. Thalidomide as an anticancer agent. J Cell Mol Med 2002;6:160-74.
9. Haslett PAJ, Corral L, Albert M et al. Thalidomide co-stimulates primary T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8+ subset. J Exp Med 1998;187:1885-92.
10. Muller GW, Chen R, Huang SY et al. Amino-substituted thaliomide analogs: potent inhibitors of TNF-α production. Boorg Med Chem Lett 1999;9:1625-1630
11. Hideshima T, Chauhan D, Shima Y et al. Thaliomide and its analogs overcome drug resistance of human multiple myeloma cells to conventional therapy. Blood 2000;96:2943-50.
12. Lentzsch S, LeBlanc R, Podar K et al. Immunomodulatory derivatives of thalidomide inhibit growth of B-cell hematological malignancies and angiogenesis *in vivo*. Leukemia 2003;17:41-4.
13. Schey SA, Fields P, Bartlett JB et al. Phase I study of an immunomodulatory thalidomide analog, CC-4047 in relapsed or refractory multiple myeloma. J Clin Oncol 2004; 22:3269-76.
14. Richardson PG, Schlossman RL, Weller E et al. Immunomodulatory drug CC-5013 overcomes drug resistance and is well tolerated in patients with relapsed multiple myeloma. Blood 2002;100:3063-7.
15. Zangari M, Tricot G, Zeldis J et al. Results of phase I study of CC-5013 for the treatment of multiple myeloma patients who relapse after high dose therapy. Blood 2001;98:775a.
16. Richardson PG, Jagannath S, Schlossman R et al. A multicenter randomized phase II study to evaluate the efficacy and safety of two CC-5013 dose regimens, when used alone or in combination with dexamethasone for the treatment of relapsed or refractory multiple myeloma. Blood 2004;100:104a.
17. Richardson PG, Jagannath S, Hussein MA et al. A multicenter single-arm open-label study to evaluate the safety and efficacy of single-agent lenalidomide in subjects with relapsed and refractory multiple myeloma. Haematologica 2005; suppl 1:154.
18. Weber DM, Chen C, Niesvizky R et al. A multicenter randomized parallel group double-blind placebo-controlled study of lenalidomide plus dexamethasone versus dexamethasone alone in previously treated subjects with multiple myeloma. Haematologica 2005; suppl 1:155.
19. Rajkumar SV, Hayman SR, Lacy MQ et al. Combination therapy with CC5013 (lenalidomide, Revlimid) plus dexamethasone (Rev/Dex) for newly diagnosed myeloma (MM) Blood 2004;102:331a.
20. List A, Kurtin S, Roe DJ et al. Efficacy of lenalidomide in myelodysplastic syndrome. N Engl J Med 2005; 352:549-557
21. Kumar S, Raje N, Hideshima T et al. Antimyeloma activity of two novel N-substituted and tetrafluorinated thalidomide analogs. Haematologica 2005; Suppl 1:159-160
22. Bartlett JB, Dredge K, Dalgleish AG. The evolution of thalidomide and its IMID derivatives as anticancer agents. Nature Reviews Cancer 2004; 4:314-22.