Drugs of the Future 2003, 28(5): 425-431

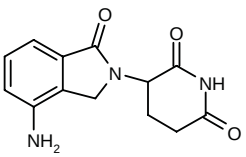
CCC: 0377-8282/2003

CC-5013

Treatment of Multiple Myeloma
Treatment of Melanoma
Treatment of Myelodysplastic Syndrome
Angiogenesis Inhibitor
TNF-α Production Inhibitor

Revimid™
CDC-5013
ENMD-0997
IMiD3

3-(4-Amino-1-oxo-1,3-dihydro-2*H*-isoindol-2-yl)piperidine-2,6-dione



$C_{13}H_{13}N_3O_3$
Mol wt: 259.2637
CAS: 191732-72-6
EN: 277395

Abstract

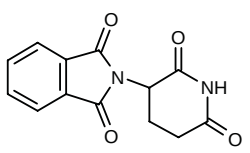
Due to its immunomodulatory activity, thalidomide has shown efficacy as a treatment in several inflammatory diseases involving increased tumor necrosis factor (TNF) levels. However, thalidomide has also been shown to be effective in noninflammatory diseases such as cancer. Thalidomide displayed potent antiangiogenic activity and has shown efficacy in trials involving patients with advanced and refractory myeloma, resulting in complete and near-complete responses and increases in survival. Unfortunately, thalidomide continues to be associated with significant adverse effects, which has prompted a search for novel potent analogues with reduced toxicity. The thalidomide analogues discovered have been classified into 2 groups: selective cytokine-inhibitory drugs (SelCIDs) and immunomodulatory drugs (IMiDs). CC-5013 has emerged as an effective IMiD, displaying TNF-α-inhibitory, antiangiogenic, cytokine-related and immunomodulatory effects more potent than thalidomide but without the adverse neurologic effects. CC-5013 has been shown to be safe and effective in phase I and II trials in patients with relapsed and refractory multiple myeloma and myelodysplastic syndrome and is now in phase III development for these indications.

Synthesis

Cyclization of *N*-(benzyloxycarbonyl)glutamine (I) by means of CDI in refluxing THF gives 3-(benzyloxycarbonylamino)piperidine-2,6-dione (II), which is deprotected with H_2 over Pd/C in ethyl acetate/4N HCl to yield 3-aminopiperidine-2,6-dione hydrochloride (III). Bromination of 2-methyl-3-nitrobenzoic acid methyl ester (IV) with NBS in CCl_4 provides 2-(bromomethyl)-3-nitrobenzoic acid methyl ester (V), which is cyclized with the aminopiperidine (III) by means of triethylamine in hot DMF to afford 3-(4-nitro-1-oxoisoindolin-2-yl)piperidine-2,6-dione (VI). Finally, the nitro group of compound (VI) is reduced with H_2 over Pd/C in methanol (1, 2). Scheme 1.

Introduction

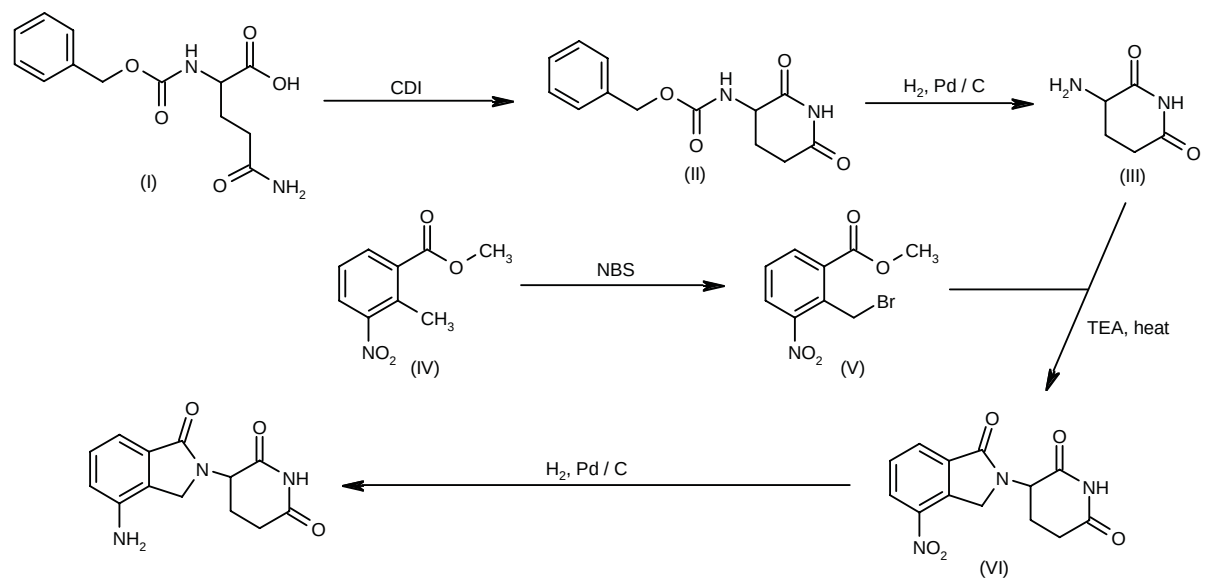
Thalidomide [I] was first synthesized in 1954 as an antihistamine and introduced as a hypnotic in 1956. The agent lacked the acute adverse events associated with other available hypnotics and was discovered to have potent antiemetic activity and later prescribed as a treatment for first-trimester morning sickness. However, thalidomide was found to be highly teratogenic and long-term treatment was associated with axonal sensorimotor neuropathy. Thalidomide was removed from the market in 1961 (3-7).



[I]

L.A. Sorbera, J. Castañer, M. Bayés. Prous Science, P.O. Box 540, 08080 Barcelona, Spain.

Scheme 1: Synthesis of CC-5013



In the early sixties, thalidomide given to patients with lepromatous leprosy (erythema nodosum leprosum, ENL) as a sedative was discovered to improve neuritis and became a standard treatment for this disease (8, 9). With the observation that ENL patients exhibited elevated serum levels of tumor necrosis factor (TNF-α) and interleukin-1β (IL-1β), it was discovered in 1991 that thalidomide selectively inhibited TNF-α production in stimulated human monocytes (10-12). As a result, thalidomide became an important immunotherapeutic agent for a number of disorders involving elevated TNF levels (13, 14).

More recently, thalidomide was shown to inhibit monocyte IL-12 production and costimulate primary human T-lymphocytes, inducing proliferation, cytokine production and cytotoxic responses in the CD8+ subset. These actions suggest that the agent could be effective as an adjuvant to promote T-cell responses in noninflammatory diseases such as cancer (15). Moreover, independent of its immunomodulatory effects, thalidomide was found to have potent antiangiogenic activity and has shown efficacy in trials involving patients with advanced cancers and refractory multiple myeloma, resulting in complete and near-complete responses and increased survival (16-18). Thalidomide was granted FDA approval as a treatment for multiple myeloma.

Multiple myeloma (myelomatosis, plasma cell myeloma or Kahler's disease) is a B-cell malignancy with mature plasma cell morphology. Plasma cells are a type of white blood cell found in bone marrow which are involved in the production of immunoglobulin. The disease is characterized by neoplastic proliferation of a single clone of plasma cells which invade bone marrow and the surrounding bone, leading to skeletal damage and causing bone pain and fractures. According to the World Health Organization, multiple myeloma is the second most common type of blood cancer with approximately 50,000 individuals from the U.S. suffering from the disease and 14,600 new cases diagnosed each year. High-dose chemotherapy together with autologous hematopoietic stem cell transplantation has become the standard treatment for the disease, although few patients are cured. There are several agents available for the treatment of multiple myeloma, as shown in Table I. Thalidomide, as mentioned above, has shown efficacy in the treatment of patients with multiple myeloma refractory to conventional high-dose chemotherapy and is now the standard treatment. Unfortunately, thalidomide continues to be associated with significant adverse effects (*e.g.*, somnolence, constipation and peripheral neuropathy) and this has prompted a search for novel potent analogues with reduced toxicity. The thalidomide analogues discovered to date have been classified into 2 groups: selective cytokine-inhibitory drugs (SelCIDs) and immunomodulatory drugs (IMiDs). SelCIDs include phosphodiesterase type 4 (PDE4) inhibitors. The mechanism of IMiDs remains unclear, although they do not inhibit PDE4. IMiDs are thought to act in a manner similar to thalidomide in stimulating T-cell proliferation and IL-2 and interferon gamma (IFN-γ) production but with enhanced efficacy (2, 19, 20). One such IMiD, CC-5013 (Revimid™), a 4-amino-substituted, small-molecule derivative of thalidomide, has emerged. It has displayed TNF-α-inhibitory, antiangiogenic cytokine-related and immunomodulatory effects that were more potent than

Table I: Drugs available and under development for the treatment of multiple myeloma (from Prous Science Integrity®).

Drug	Source	Phase
Bortezomib	Millennium	L-2003
Thalidomide*	Celgene/Pharmion	Prereg
Doxil®*	Alza (Johnson & Johnson)	III
Minodronic acid	Yamanouchi	III
Oblimersen sodium	Genta	III
CC-5013	Celgene	III
Vinorelbine*	Pierre Fabre/Kyowa Hakko	III
^{166}Ho-DOTMP	NeoRx	II
2-Methoxyestradiol	EntreMed	II
AE-941	AEterna	II
Alvocodib hydrochloride	Aventis/NCI	II
Arsenic trioxide*	Cell Therapeutics	II
Atlizumab	Chugai	II
Gallium maltolate	Titan	II
NSC-637037	NCI	II
PI-88	Progen	II
ZD-6474	AstraZeneca	II
Actimid™	Celgene	I/II
β-Alethine	LifeTime/Dovetail	I/II
BrevaRex™	AltaRex	I/II
GVAX™	Cell Genesys	I/II
AHM	Chugai	I
ENMD-0995	Celgene	I
LymphoRad 131	Human Genome Sciences	I
TRAIL-R1 MAb	Cambridge Antibody Technology	I

*Launched for another indication

thalidomide but the agent lacked the unwanted neurologic effects. CC-5013, therefore, was chosen for further development as a treatment for relapsed or refractory multiple myeloma.

Pharmacological Actions

In *in vitro* experiments using lipopolysaccharide (LPS) stimulated human peripheral blood mononuclear cells (PBMCs), CC-5013 potently inhibited TNF-α (IC_{50} = 100 nM *vs.* about 200 μM for thalidomide) but was ineffective (up to 100 μM) in inhibiting PDE4 enzymes isolated from U-937 cells. Only a modest decrease in TNF-α-inhibitory activity was observed for the agent in experiments using LPS-stimulated whole blood (IC_{50} = 480 nM) to mimic *in vivo* conditions (2).

CC-5013 and thalidomide were also shown to have enhancing effects on TNF-α production in an *in vitro* study using human PBMCs and whole blood which examined the effects of CC-5013 on expression of TNF-α and its receptor TNFR2 during costimulation of CD4+ and CD8+ T-cells. CC-5013 decreased surface expression of TNFR2 on both anti-CD3-stimulated CD4+ and CD8+ T-cells, which led to a reduction in soluble TNFR2 levels; this effect correlated with induction of the surface IL-2 receptor, CD25. However, treatment had no effect on total TNFR2 protein expression suggesting that the agent was inhibiting trafficking of the receptor to the membrane. Costimulation with CC-5013 also resulted in an increase in TNF-α production by both T-cell subsets. This costimulation was IL-2-dependent although the inhibitory effects on TNFR2 were not. Thalidomide exhibited effects similar to CC-5013. Interestingly, serum TNF-α levels were found to be elevated in CC-5013-treated (5 mg/day p.o. for 1 week escalated to 10, 25 and 50 mg/day at weeks 2, 3 and 4, respectively, and continued) patients with advanced cancer involved in a phase I trial. Thus, in addition to the TNF-inhibitory effects observed during inflammatory stimuli (*i.e.*, LPS-stimulated monocytes/macrophages), CC-5013 costimulation of CD4+ and CD8+ T-cells resulted in superinduction of TNF-α production, an effect also evident in the clinic (21).

CC-5013 was shown to have an antiangiogenic action in studies where the agent (10 μg/ml) significantly inhibited angiogenesis in human umbilical vein endothelial cells (HUVEC) *in vitro*. Significant reductions in tubule development were also observed at a concentration of 1 μg/ml. Although CC-5013 had no significant effects on basic fibroblast growth factor (bFGF)- and vascular endothelial growth factor (VEGF)-induced proliferation (IC_{50} = 50 μg/ml or more) of HUVEC, it significantly inhibited migration of EA.hy.926 cells in an *in vitro* wound healing assay, suggesting that inhibition of angiogenesis may be via inhibition of normal migratory processes. CC-5013 displayed marked antiangiogenic effects in a rat aorta assay. A dose of 1 μg, significantly inhibited microvessel outgrowths by day 4 of culture (100% at 10 μg/ml). In contrast, thalidomide (up to 50 μg/ml) had no significant effects. The agent was confirmed to have no significant

activity on PDE4 (isolated from U-937 cells; IC_{50} = 100 μM or more) (22).

The potent antiangiogenic effect of CC-5013 was also demonstrated *in vivo* in nude mice bearing murine colorectal tumors (CMT93 cell line). Significant reductions in tumor growth were observed with doses of 10 and 50 mg/kg/day i.p. (starting when tumors were 20 mm^3). Histological analysis of tumors from treated animals revealed large areas of necrotic tissue (22).

The immunomodulatory and antitumor activity of CC-5013 was further investigated *in vitro*. The effects of the agent on VEGF-initiated clonogenic responses, receptor phosphorylation and signaling in myeloid malignant cells and on hematopoietic progenitor formation in bone marrow specimens from normal volunteers and patients with myelodysplastic syndrome (MDS) were examined. CC-5013 concentration- (10 μM and greater) and time-dependently inhibited rhu-VEGF-induced clonogenic responses and blocked cytokine-induced recruitment of cells into the cell cycle at S+G2/M in HL-60 (VEGF receptor [VEGFR]-1+) and KG-1 (VEGFR-1/2+) cells. Treatment had no effect on phosphorylation of VEGFR-induced extracellular signal-related protein kinases ERK-1 and ERK-2 but was found to suppress cytokine-induced PI3-kinase/Akt. Moreover, CC-5013 in a lineage- and concentration-dependent manner inhibited committed progenitor formation in MDS but not normal bone marrow specimens; while concentrations of 0.001-10 μM inhibited primitive progenitor (CFU-GEMM, BFU-E) growth by 25-90%, inhibition of myeloid progenitor recovery was observed at concentrations greater than 100 μM (23).

Results from further *in vitro* studies revealed that CC-5013 has the ability to both directly and indirectly (via IL-2 from T-cells) activate natural killer (NK) cells separated from normal donor PBMCs. The agent (1 μM for 5 days) also enhanced NK cell killing of multiple myeloma cells (K-562, U266) and IL-2 production from T-cells (3.7-fold); T-cell IL-12 and IL-15 production was not affected by the agent. Treatment of PBMCs with CC-5013 increased CD56+ cells by 1.3-fold and NK cell activity by 1.6-fold. A role for IL-2 in CC-5013 action was suggested since both an anti-IL-2 receptor antibody and ciclosporin blocked CC-5013-induced activation of NK cells. It was concluded that the immunomodulatory activity of CC-5013 could contribute to increasing autologous anti-multiple myeloma immunity (24).

The mechanism of action involved in CC-5013-induced apoptosis of multiple myeloid cells (MM.1S, OCI-My-5) was examined in an *in vitro* study. Results showed that the agent activated caspase 8 (but not caspase 9), enhanced cell sensitivity to Fas-mediated apoptosis and downregulated NF-κB activity and apoptosis protein-2 and FLICE inhibitory protein expression (25).

In addition to its antitumor efficacy, CC-5013 was also demonstrated to be a potentially effective adjunct to antituberculous meningitis therapy. In an *in vivo* study using a rabbit model of experimental tuberculosis meningitis (intracisternal inoculation with *Mycobacterium bovis* resulting in mortality by day 28), treatment with antituberculous agents (30 mg/day isoniazid i.m. and rifampin p.o. starting on postinfection day 17 and continuing until day 28) alone or in combination with thalidomide (200 mg/day p.o. starting on postinfection day 16 and continuing until day 28) improved the clinical course of the disease and increased survival by approximately 50% as compared to controls. In contrast, treatment with antituberculous agents in combination with CC-5013 (50 mg/day p.o. starting on postinfection day 16 and continuing until day 28) markedly improved survival by 73% and attenuated meningeal inflammation, in addition to limiting pathological neurological alterations and reducing leukocytosis in cerebrospinal fluid (CSF) and TNF in CSF and plasma (26).

Pharmacokinetics

The safety and pharmacokinetics of CC-5013 (100 mg on day 1 and b.i.d. on days 2-8) were determined in a single-blind, placebo-controlled, multiple-dose study conducted in 8 healthy male volunteers. Two patients discontinued due to dermatological adverse events. Absorption of the agent was rapid on days 1 and 8, with C_{max} (1618 and 1568 ng/ml, respectively) achieved at 1 h. Steady-state plasma levels were reached by day 4. Terminal $t_{1/2}$ values on days 1 and 8 were 3.5 and 7.6 h, respectively. Very little accumulation of the agent was observed after multiple dosing. Multiphasic elimination was observed where plasma levels first rapidly decreased (6-20%). Renal clearance (190 and 220 ml/min on days 1 and 8, respectively) was greater than the glomerular filtration rate (*i.e.*, renal secretion), with 68% of the dose excreted as the unchanged compound (27).

A phase I double-blind, single-ascending-dose study (5-400 mg under fasting conditions and 200 mg in the fed state) conducted in 19 healthy males reported no serious adverse events. Fifteen subjects completed the study. Absorption of the agent was rapid. AUC values increased dose-proportionately and disposition appeared to be multiphasic. Food intake did not alter AUC values although it decreased C_{max} values by 39% and increased t_{max} values by 75%. The elimination $t_{1/2}$ value increased with dose and was longer in the fed state. Good distribution and rapid clearance were observed. Urinary clearance was high (but 27% lower in the fed state), with 67% of the dose recovered unchanged. Renal clearance was 190 ml/min (28).

Clinical Studies

A single-center, open-label, escalating-dose phase I trial conducted in 15 patients with multiple myeloma who relapsed after at least 1 high-dose chemotherapy regimen examined the safety and efficacy of CC-5013 (5, 10, 25 or 50 mg/day for 4 weeks). Although no responses were observed at the 5- and 10-mg dose levels, 2 patients starting on 10 mg/day and escalated to 25 and

Table II: Clinical studies of CC-5013 (from Prous Science Integrity®).

Indication	Design	Treatments	n	Conclusions	Ref.
Multiple myeloma	Open	CC-5013, 5 mg po od x 4 wk CC-5013, 10 mg po od x 4 wk CC-5013, 25 mg po od x 4 wk CC-5013, 50 mg po od x 4 wk	15	CC-5013 showed antitumor activity in patients with refractory myeloma, but was also associated with myelosuppression and cardiovascular problems	29
Multiple myeloma	Open	CC-5013, 5 mg/d po [adjusted according to toxicity] x 4 wk (n=3) CC-5013, 10 mg/d po [adjusted according to toxicity] x 4 wk (n=6) CC-5013, 25 mg/d po [adjusted according to toxicity] x 4 wk (n=3) CC-5013, 50 mg/d po [adjusted according to toxicity] x 4 wk (n=13)	25	CC-5013 showed activity for the treatment of relapsed multiple myeloma; the maximal tolerated dose was 25 mg/d	30
Pancreatic cancer, malignant melanoma	Open	CC-5013, 5-50 mg od x 4 wk	20	CC-5013 was well tolerated and showed evidence of antitumor activity, promoting T-cell activation and increasing the plasma levels of cytokines (*e.g.*, GM-CSF, IL-12 and TNF-α) in patients with advanced cancer	31
Multiple myeloma	Randomized, multicenter	CC-5013, 15 mg po bid x 3 wk [in cycles of 4 wk] + [after 4 wk if progression or 8 wk if stabilization] + Dexamethasone, 40 mg po od 4x/2 wk CC-5013, 30 mg po bid x 3 wk [in cycles of 4 wk] + [after 4 wk if progression or 8 wk if stabilization] + Dexamethasone, 40 mg po od 4x/2 wk	34	CC-5013 was effective and well tolerated in patients with refractory and relapsed multiple myeloma	32
Myelodysplastic syndrome	Open	CC-5013, 25 mg [reduced to 10 mg due to adverse events] po od x 16 wk (n=10) CC-5013, 10 mg po od x 16 wk (n=5)	15	A daily oral dose of CC-5013 10 mg was well tolerated and induced erythropoietic remission in patients with myelodysplastic syndrome	35

50 mg/day, respectively, achieved a greater than 50% decrease in paraprotein; one of these patients continued to have less than 5% bone marrow plasma cells while the other experienced at 50% reduction in bone marrow plasmacytosis. A patient given 25 mg/day had stable paraprotein and bone marrow plasmacytosis for 5 months. Two patients discontinued due to syncope and disease progression, respectively, and 2 patients receiving 50 mg/day experienced dose-limiting toxicities of thromboembolism and severe thrombocytopenia. Although neurologic toxicity was minimal, it was concluded that the agent can cause significant myelosuppression even in patients with sufficient platelet counts and bone marrow cellularity at study onset. In addition, cardiovascular toxicities were also associated with treatment (29). The results of this study and some of those that follow are summarized in Table II.

A phase I dose-escalation study conducted in 27 patients with relapsed and refractory relapsed multiple myeloma (who failed at least 2 prior regimens) demonstrated the safety and efficacy of CC-5013 (5, 10, 25 and 50 mg once daily for 4 weeks followed by accrual). No dose-limiting toxicity was observed with any dose during the first 28 days in the 24 evaluable patients, although grade 3 myelosuppression was reported in 13 patients treated with 50 mg/day after day 28. Because a dose reduction to 25 mg/day was well tolerated in 12 patients, it was concluded to be the maximum tolerated dose (MTD). No significant somnolence, constipation or neuropathy was observed in any of the treatment groups. The best responses (at least a 25% reduction in paraprotein) were observed in 17 (71%) patients (including 11 who had previously received thalidomide); 7 patients experienced at least a 50% reduction in paraprotein. Stable disease (less than 25% decrease in paraprotein) was seen in 2 (8%) patients (30).

The efficacy, tolerability and safety of CC-5013 (5 mg/day escalated to 50 mg/day for 4 weeks) were evaluated in 20 heavily pretreated patients with advanced stage IV malignant myeloma (n=13), pancreatic (n=2) and other cancers (n=5). The agent was generally well tolerated with no serious adverse events reported. Fourteen patients completed the trial, with 3 discontinuing due to disease progression and 3 to withdrawal of consent. Analysis of peripheral T-cell surface markers *in vitro* revealed that all patients had evidence of activation of CD4+ and CD8+ T-cells (*i.e.*, increase in CD45RO+ expression). In addition, some patients had activation of

memory cells (*i.e.*,CD45RA+/L-selectin$_{low}$), possibly indicating activation of tumor-specific cells. Analysis of serum cytokine and proangiogenic factors indicated that the possible activation of tumor-specific cells was associated with increased serum GM-CSF, sIL-2Rα, IL-12 and TNF-α levels; no alterations in proangiogenic factors were observed with treatment. It was concluded that the treatment-related induction of immune activation observed may be more beneficial in less advanced cancer patients where CC-5013 could be used as an immunostimulatory adjuvant with other chemotherapy regimens (31).

The efficacy and safety of CC-5013 (15 mg b.i.d. or 30 mg once daily p.o. for 3 weeks with 1 week of rest) alone or in combination with dexamethasone (40 mg/day p.o. for 4 days every 2 weeks in patients with progressive disease at 4 weeks and in patients with stable disease at 8 weeks) were demonstrated in a multicenter, randomized phase II trial involving 70 patients with refractory or relapsed multiple myeloma. Of the 46 patients evaluable for response, complete, partial (greater than 50% reduction in paraprotein) and minimal (greater than 25% reduction) responses were observed in 2, 8 and 15 patients, respectively. Fourteen patients had stable disease and 7 had disease progression. Of the 7 patients with disease progression, 4 achieved a minimal response and 1 had stable disease when subsequently treated with CC-5013 in combination with dexamethasone. Response rates were similar with both dosing regimens, although the 30-mg-once-daily schedule was concluded to be better tolerated since 11 patients receiving 15 mg b.i.d. experienced grade 3 or 4 myelosuppression requiring dose reduction, as compared to only 4 patients in the 30-mg-once-daily group. Grade 3 neuropathy was reported in 1 patient on the 30-mg-once-daily dosing schedule who had previously experienced grade 2 neuropathy with another treatment regimen. Other adverse events observed were grade 1 or 2 diarrhea, fever, muscle cramps, neuropathy, constipation, rash and fatigue (32-34).

A phase I/II trial conducted in 23 patients with myelodysplastic syndrome (MDS) (including 17 with early-stage MDS, 19 dependent on regular red blood cell transfusions and 7 who failed previous thalidomide therapy) reported that of the 16 evaluable patients treated with CC-5013 (25 mg daily p.o), 9 had an erythroid response (*i.e.*, became transfusion-independent, had a greater than 50% reduction in red blood cell transfusions or had an increase in hemoglobin of 3 g/dl). Median response duration was at least 29 weeks. Five patients had a platelet response and 5 of 8 patients with abnormal cytogenetics had complete disappearance of abnormalities. Moreover, 5 of 5 patients with deletion of chromosome 5q31-33 achieved a complete erythroid response and disappearance of the abnormal bone marrow clone. Eight of 11 patients with refractory anemia or refractory anemia with ringed sideroblasts and 9 of 13 patients with low- or intermediate-risk MDS experienced erythroid responses, indicating a possibly greater benefit in patients with early-stage MDS. All patients receiving the 25 mg/day dose required dose reductions to 10 or 5 mg/day due to myelosuppression. Fatigue and pneumonia were also reported. It was concluded that the 10 mg/day dose was well tolerated, with only minimal myelosuppression (35, 36).

CC-5013 has received fast track designation from the FDA for the treatment of relapsed or refractory multiple myeloma (33) and myelodysplastic syndromes (37). The compound is under phase III clinical development for multiple myeloma and metastatic malignant melanoma and is also being evaluated as a potential treatment for hematological and solid tumors and inflammatory diseases (38).

Source

Celgene Corp. (US).

References

1. Muller, G.W., Stirling, D.I., Chen, R.S.-C. (Celgene Corp.). *Substd. 2-(2,6-dioxopiperidin-3-yl)-phthalimides and -1-oxoisoindolines and method of reducing TNFα levels.* EP 0925294, US 5635517, WO 9803502.

2. Muller, G.W., Chen, R., Huang, S.Y., Corral, L.G., Wong, L.M., Patterson, R.T., Chen, Y., Kaplan, G., Stirling, D.I. *Amino substituted thalidomide analogs: Potent inhibitors of TNF-α production.* Bioorg Med Chem Lett 1999, 9: 1625-30.

3. Botting, J. *The history of thalidomide.* Drug News Perspect 2002, 15: 604-11.

4. Sommer, C. *Thalidomide as a blocker of TNF production.* Drugs Fut 1999, 24: 67-75.

5. Mellin, G., Katzenstein, M. *The saga of thalidomide.* New Engl J Med 1962, 267: 1184-93.

6. Fullerton, P.M., Kremer, M. *Neuropathy after intake of thalidomide.* BMJ - Br Med J 1961, 2: 855-8.

7. Pfeiffer, R.A., Kosenow, W. *Thalidomide and congenital abnormalities.* Lancet 1962, 1: 45.

8. Sheskin, J. *Thalidomide in the treatment of lepra reactions.* Clin Pharmacol Ther 1965, 6: 303-6.

9. Barnhill, R., McDougall, A. *Thalidomide: Use and possible mode of action in reactional lepromatous leprosy and in various other conditions.* J Am Acad Dermatol 1982, 7: 317-23.

10. Sarno, E.N., Grau, G.E., Vieira, L.M., Nery, J.A. *Serum levels of tumour necrosis factor-α and interleukin-1β during leprosy reactional states.* Clin Exp Immunol 1991, 84: 103-8.

11. Sampaio, E.P., Sarno, E.N., Galilly, R., Cohn, Z.A., Kaplan, G. *Thalidomide selectively inhibits tumor necrosis factor a production by stimulated human monocytes.* J Exp Med 1991, 173: 699-703.

12. Barnes, P.F., Chatterjee, D., Brennan, P.J., Rea, T.H., Modlin, R.L. *Tumor necrosis factor production in patients with leprosy.* Infect Immun 1992, 60: 1441-6.

13. Marriott, J.B., Muller, G., Dalgleish, A.G. *Thalidomide as an emerging immunotherapeutic agent.* Immunol Today 1999, 20: 538-40.

14. Raje, N., Anderson, K. *Thalidomide - a revival story*. New Engl J Med 1999, 341: 1606-9.

15. Haslett, P.A., Corral, L.G., Albert, M., Kaplan, G. *Thalidomide costimulates primary human T lymphocytes, preferentially inducing proliferation, cytokine production, and cytotoxic responses in the CD8$^+$ subset.* J Exp Med 1998, 187: 1885-92.

16. Singhal, S., Mehta, J., Desikan, R. et al. *Antitumor activity of thalidomide in refractory multiple myeloma.* New Engl J Med 1999, 341: 1565-71.

17. Barlogie, B., Desikan, R., Eddlemon, P. et al. *Extended survival in advanced and refractory multiple myeloma after single-agent thalidomide: Identification of prognostic factors in a phase 2 study of 169 patients.* Blood 2001, 98: 492-4.

18. Neben, K., Moehler, T.M., Benner, A., Kraemer, A., Ho, A.D., Goldschmidt, H. *Dose-dependent effect of thalidomide (THAL) on overall survival (OS) in relapsed and refractory multiple myeloma (MM).* Blood 2001, 98(11, Part 1): Abst 690.

19. Corral, L.G., Haslett, P.A., Muller, G.W., Chen, R., Wong, L.-M., Ocampo, C.J., Patterson, R.T., Stirling, D.I., Kaplan, G. *Differential cytokine modulation and T cell activation by two distinct classes of thalidomide analogues that are potent inhibitors of TNF-α.* J Immunol 1999, 163: 380-6.

20. Moreira, A.L., Corral, L.G., Ye, W., Johnson, B., Stirling, D., Muller, G.W., Freedman, V.H., Kaplan, G. *Thalidomide and thalidomide analogs reduce HIV type 1 replication in human macrophages in vitro.* AIDS Res Hum Retroviruses 1997, 13: 857-63.

21. Marriott, J.B., Clarke, I.A., Dredge, K., Muller, G., Stirling, D., Dalgleish, A.G. *Thalidomide and its analogues have distinct and opposing effects on TNF-α and TNFR2 during co-stimulation of both CD4$^+$ and CD8$^+$ T cells.* Clin Exp Immunol 2002, 130: 75-84.

22. Dredge, K., Marriott, J.B., Macdonald, C.D., Man, H.-W., Chen, R., Muller, G.W., Stirling, D., Dalgleish, A.G. *Novel thalidomide analogues display anti-angiogenic activity independently of immunomodulatory effects.* Br J Cancer 2002, 87: 1166-72.

23. List, A.F., Tate, W., Glinsmann-Gibson, B.J., Baker, A. *The immunomodulatory thalidomide analog, CC5013, inhibits trophic response to VEGF in AML cells by abolishing cytokine-induced PI3-kinase/Akt activation.* Blood 2002, 100(11, Part 1): Abst 521.

24. Hayashi, T., Hideshima, T., Akiyama, M., Munshi, N., Chaudhan, D., Anderson, K.C. *Mechanisms whereby immunomodulatory analogs of thalidomide augment autologous NK cell anti-myeloma immunity.* Blood 2002, 100(11, Part 1): Abst 3219.

25. Mitsiades, N., Mitsiades, C.S., Poulaki, V., Chauhan, D., Richardson, P.G., Hideshima, T., Munshi, N.C., Treon, S.P., Anderson, K.C. *Apoptotic signaling induced by immunomodulatory thalidomide analogs in human multiple myeloma cells: Therapeutic implications.* Blood 2002, 99: 4525-30.

26. Tsenova, L., Mangaliso, B., Muller, G., Chen, Y., Freedman, V.H., Stirling, D., Kaplan, G. *Use of IMiD3, a thalidomide analog, as an adjunct to therapy for experimental tuberculous meningitis.* Antimicrob Agents Chemother 2002, 46: 1887-95.

27. Scheffler, M.R., Thomas, S., Harden, J., Oliver, S.D., Teo, S.K. *Safety and pharmacokinetics of CDC-501, a novel immunomodulatory-oncologic agent, after single then multiple, oral 100 mg twice daily doses.* Clin Pharmacol Ther 2002, 71(2): Abst WPIII-63.

28. Teo, S.K., Oliver, S., Harden, J., Stirling, D., Thomas, S., Scheffler, M. *A phase I, single-blind, placebo-controlled, ascending single oral dose, safety, tolerability and pharmacokinetic study of CDC-501, a novel immunomodulatory-oncologic agent, in healthy male subjects with a comparison of fed and fasted.* Clin Pharmacol Ther 2002, 71(2): Abst WPIII-64.

29. Zangari, M., Tricot, G., Zeldis, J., Eddlemon, P., Saghafifar, F., Barlogie, B. *Results of phase I study of CC-5013 for the treatment of multiple myeloma (MM) patients who relapsed after high dose chemotherapy (HDCT).* Blood 2001, 98(11, Part 1): Abst 3226.

30. Richardson, P.G., Schlossman, R.L., 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.

31. Marriott, J.B., Clarke, I.A., Dredge, K., Pandha, H., Kristaleit, H., Polychronis, A., Muller, G.W., Stirling, D., Dalgleish, A.G. *Thalidomide analogue CDC-501 is safe and well tolerated by patients with end stage cancer and shows evidence of clinical responses and extensive immune activation.* Br J Cancer 2002, 86(Suppl. 1): Abst 6.4.

32. Richardson, P., Jagannath, S., Schlossman, R. et al. *A multicenter, randomized, phase II study to evaluate the efficacy and safety of two CDC-5013 dose regimens when used alone or in combination with dexamethasone (Dex) for the treatment of relapsed or refractory multiple myeloma (MM).* Blood 2002, 100(11, Part 1): Abst 386.

33. *Revimid™ monotherapy induces reduction or stabilization of paraprotein levels in eighty-five percent of advanced multiple myeloma patients in phase II trial.* Celgene Corp. Press Release December 9, 2002.

34. *Revimid granted fast track designation for relapsed or refractory multiple myeloma.* DailyDrugNews.com (Daily Essentials) February 6, 2003.

35. List, A.F., Kurtin, S.E., Glinsmann-Gibson, B.J., Bellamy, W.T., Buresh, A.J., Waddleton, D., Knight, R. *High erythropoietic remitting activity of the immunomodulatory thalidomide analog, CC5013, in patients with myelodysplastic syndrome (MDS).* Blood 2002, 100(11, Part 1): Abst 353.

36. *First data on Revimid™ in myelodysplastic syndromes demonstrates fifty-six percent of patients achieved hematological response.* Celgene Corp. Press Release December 10, 2002.

37. *Revimid granted fast track status for myelodysplastic syndromes.* DailyDrugNews.com (Daily Essentials) April 17, 2003.

38. *Celgene summarizes recent clinical development highlights.* DailyDrugNews.com (Daily Essentials) January 10, 2003.