# Thalidomide Chemotherapy-Induced Peripheral Neuropathy: Actual Status and New Perspectives with Thalidomide Analogues Derivatives

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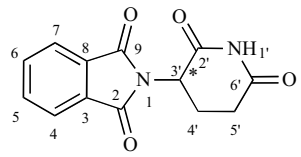
**Abstract:** IMiDs compounds are a class of analogues of thalidomide, with greater immunomodulatory activity and a superior safety profile compared to the parent compound. They show substantial increase in potency and an interesting tolerability profile, primarily due to a decreased incidence of the most severe side effect of thalidomide, i.e. Chemotherapy-Induced Peripheral Neurotoxicity (CIPN). These novel aspects of the IMiDs compounds will be discussed.

**Key Words:** IMiDs, thalidomide, CC-5013, lenalidomide, CC-4047, pomalidomide, safety, side effects, CIPN.

## INTRODUCTION

Thalidomide, N-(2,6-dioxo-3-piperidyl)phthalimide or α -*N*-phthalimido-glutarimide, Fig. (**1**), was first introduced into European markets in the 1950s as a sleep aid and antiemetic drug for pregnant women. It was withdrawn from the market soon thereafter when its teratogenic effects were discovered. It has re-emerged recently as an effective treatment for several dermatologic, gastrointestinal, and oncologic conditions. In 1998 U.S. Food and Drug Administration (FDA) granted approval to thalidomide for the treatment of erythema nodosum leprosum [1], a debilitating and disfiguring complication of leprosy, and in May 2006 for use in combination with dexamethasone in newly diagnosed multiple myeloma (MM) patients [2]. To minimize the risk of foetal exposure to thalidomide Celgene (Celgene Corporation, Warren, New Jersey) has developed a comprehensive program to control and monitor the drug's prescribing, dispensing and use of thalidomide [3]. This program, known as the System for Thalidomide Education and Prescribing Safety (STEPS™) uses a tree-pronged approach: (1) controlling access to the drug; (2) educating prescribers, pharmacists and patients; and (3) monitoring compliance.

Peripheral nervous system damage (Chemotherapy-Induced Peripheral Neurotoxicity, CIPN) is now recognized as one of the most significant side effects of this medication. The most common presentation is distal paresthesias and/or dysesthesias with or without sensory loss. Physical examination may be normal or show mild reduction in sensation in distal limbs. Strength is usually preserved although mild weakness may be present. Reflexes, particularly ankle jerks, may be depressed or absent. Symptoms are progressive, usually beginning in distal lower limbs but later extending proximally and into upper extremities. Symptoms can be disabling and often necessitate discontinuation of the drug despite disease control. Onset is usually delayed (up to 1 year in most cases) after initiating thalidomide. On neuro




**1**

**Fig. (1).** Structural formula of thalidomide.

physiological basis, reduction in sensory nerve action potential amplitude with relative preservation of conduction velocities and compound motor action potentials are typical findings [4], suggesting a sensory axonal neuropathy as the predominant pathological event.

Alternatively, some evidence suggests that thalidomide may cause also a neuronopathy. In these patients the clinical presentation is rather different, with an early involvement of all four limbs. Nerve conduction studies in these cases show isolated reduction in the amplitude of sensory nerve action potentials in all limbs and somatosensory evoked potentials have prolonged spinal and cortical latencies. T2 hyperintense, non–mass-like, non-enhancing lesions may be seen in the posterior columns of the spinal cord on MRI, indicating the involvement of the centripetal branch of the primary sensory neuron axons. Such cases may occur with less cumulative dose of thalidomide exposure [4, 5]. However, conflicting results regarding the relationship of thalidomide dosage and incidence of neuropathy still exist. Although some studies found a relationship between cumulative dosage and occurrence of neuropathy [6, 7], others failed to do so [8-10]. Cavaletti *et al*. [7] noted a dose relationship beginning at cumulative doses of 20 g. In several studies that failed to identify a dose relationship, median doses were below this level [8, 10]. Alternatively, increased risk of CIPN have has been related to daily dose of thalidomide [10]. Frequently, neuropathic symptoms may improve with discontinuation of thalidomide [4, 6].

Pre-existing neuropathy in patients treated with thalidomide may be due to the underlying condition (e.g., MM or lupus erythematosus) or previous/concurrent treatments (e.g.,

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vincristine). Risk factors for neuropathy in thalidomide-treated patients have not been elucidated and most studies failed to find a correlation between age, thalidomide administration and occurrence of CIPN [8-10]. Preliminary clinical data suggest that thalidomide analogues CC-5013, lenalidomide, and CC-4047, pomalidomide, are more potent and have a better toxicity profile, including reduced risk of inducing CIPN.

## THALIDOMIDE: A COMPLEX BALANCE BETWEEN CHEMISTRY, METABOLISM, AND HYDROLYSIS

The structure of thalidomide, **1**, is characterized by a 3-substituted glutarimide ring (2,s-piperidinedione ring; carbons numbered 1' - 6') and a phthalimide ring (1,3-isoindolinedione ring; carbons numbered 1 - 9). Both rings, especially the phthalimide ring, are prone to hydrolysis, *in vivo* or *in vitro*. Fig. (**2**) depicts 12 hydrolysis products of thalidomide and their routes of degradation [11, 12]. These compounds, **Table 1**, are non-enzymatically formed in aqueous solution under physiological conditions. Moreover, thalidomide is racemic and it contains both left (L)- and right (R)-handed isomers in equal amounts. Only the (S) enatiomer is teratogenic and causes birth defects, but since the enantiomers are rapidly interconverted, in vivo administering only one enantiomer will not prevent the teratogenic effect in humans. The four amide bonds in thalidomide allow for simple and rapid hydrolysis. In addition, thalidomide is racemic and rapidly interconverts between two confirmed enantiomers. Furthermore, hydrolysis products with intact phthalimido or glutarimide rings can potentially be further metabolized via cytochrome P450, although this pathway has not been confirmed yet. As a result, over 100 different compounds can theoretically form. Pharmacokinetic studies of thalidomide have identified three hydrolysis products in human plasma using liquid chromatography-mass spectrometry; α-(*o*-carboxybenzamido) glutarimide **2**, 2-phthalimidoglutaramic acid **3** and 4- phthalimidoglutaramic acid **4** [13]. These hydrolysis products were also found in human urine.The same metabolite profile was observed in mouse plasma and urine following both oral and intravenous ad-

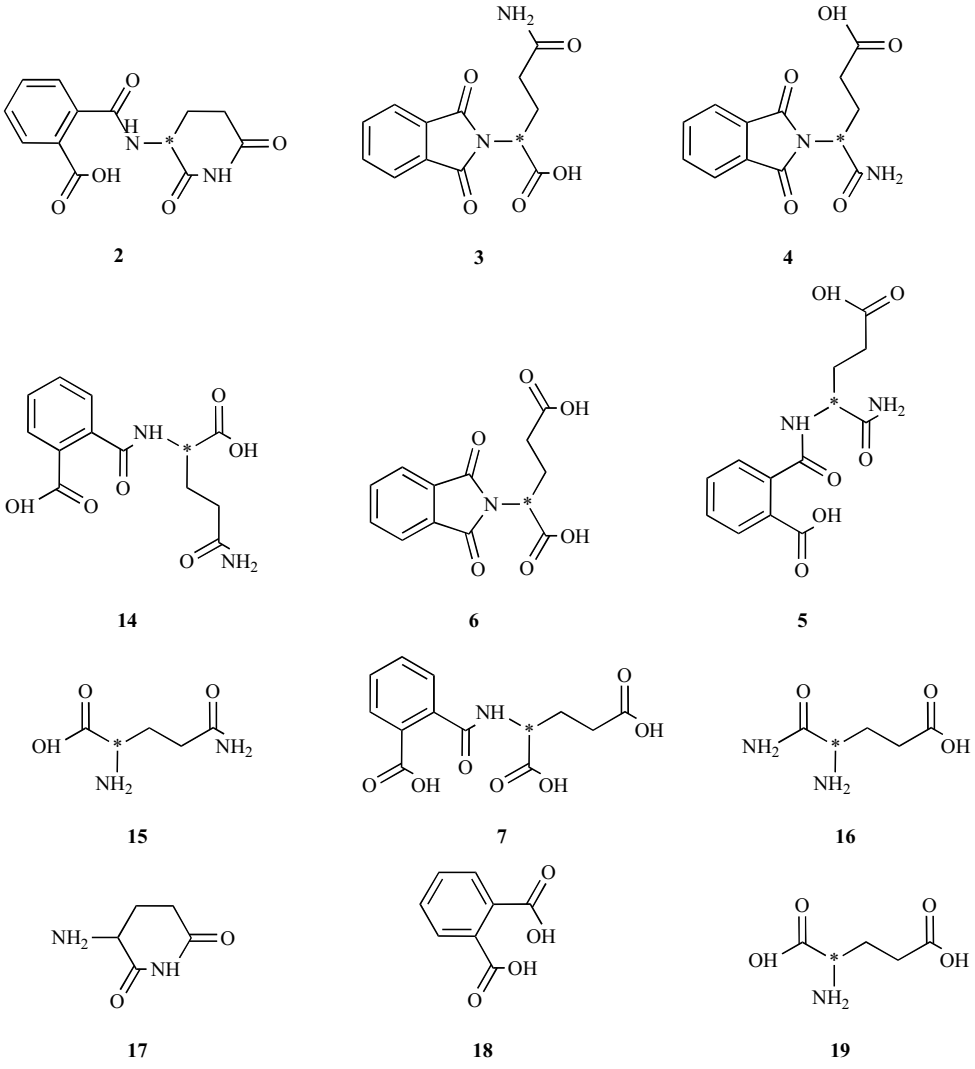



**Fig. (2).** Structural formula of products formed by non-enzymatic hydrolysis of thalidomide [12].

**Table 1. Products Formed by Non-Enzymatic Hydrolysis of Thalidomide [12]**

| | | | | | |
|---|---|---|---|---|---|
| **2** | α-(*o*-carboxybenzamido)glutarimide | | **14** | 2-(*o*-carboxybenzamido)glutaramic acid | |
| **3** | 2-phthalimidoglutaramic acid | *phthaloylglutamine* | **15** | 2-aminoglutaramic acid | *glutamine* |
| **4** | 4-phthalimidoglutaramic acid | *phthaloylisoglutamine* | **16** | 4-aminoglutaramic acid | *isoglutamine* |
| **5** | 4-(*o*-carboxybenzamido)glutaramic acid | | **17** | α-aminoglutaramide | |
| **6** | 2-phthalimidoglutaric acid | *phthaloylglutamic acid* | **18** | phthalic acid | |
| **7** | 2-(*o*-carboxybenzamido)glutaric acid | | **19** | 2-aminoglutaric acid | *glutamic acid* |

ministration, with the addition of 4-(*o*-carboxybenzamido) glutaramic acid **5** in urine. Studies administering radiolabelled thalidomide were carried out in the 1960's and similarly found α-(*o*-carboxybenzamido)gluta-rimide **2** to be the major hydrolysis product in man, followed by 4-phthalimidoglutaramic acid **4** [11, 14]. The remaining hydrolysis products have not been identified in humans, but are produced when thalidomide is in aqueous solution [15-18]. All 12 products can be formed at pH 7.4, but only the phthalimide ring is cleaved, resulting in α-(*o*-carboxybenz-amido) glutarimide **2**, between pH 6.0 and 7.0 [17]. The rate of hydrolysis is highly dependent on pH, with hydrolysis occurring much more slowly at lower pH. Early experiments demonstrated a half-life of 2.4 hours for thalidomide *in vitro* at pH 7.4 and 37° C, resulting in the primary hydrolysis products α-(*o*-carboxybenzamido)gluta-rimide **2**, 2-phthalimidoglutaramic acid **3** and 4-phthalimido-glutaramic acid **4**, which are significantly more stable in solution [16].

In addition to spontaneous hydrolysis, thalidomide undergoes enzymatic metabolism, albeit to a lesser extent, and this has been the subject of extensive investigation over several years. A series of *in vitro* and *in vivo* studies have been performed to elucidate the structures of the metabolites formed, identify the enzymes responsible for their production and assess interspecies differences in metabolism, which may account for interspecies differences in the biological effects of thalidomide. The structures of some of the thalidomide metabolites (both confirmed and proposed in the literature) that can be formed by enzyme-mediated metabolism are depicted in Fig. (**3**). Most attention has focused

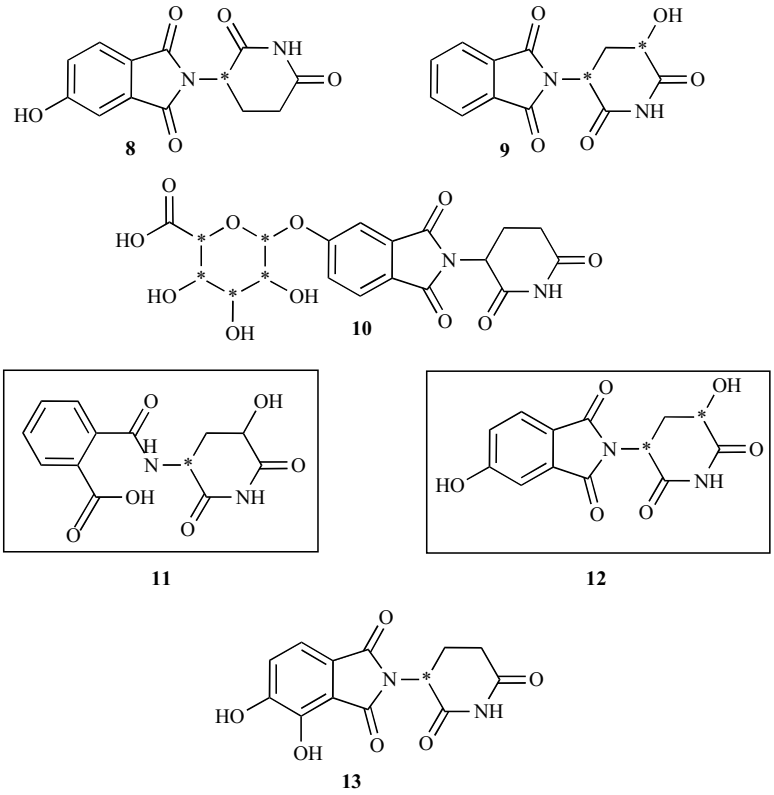



**Fig. (3).** Structural formula of products formed by enzymatic metabolism of thalidomide. Metabolite structures that have been proposed in the literature but not yet confirmed are within a box [12].

**Table 2. Products Formed by Enzymatic Metabolism of Thalidomide [12]**

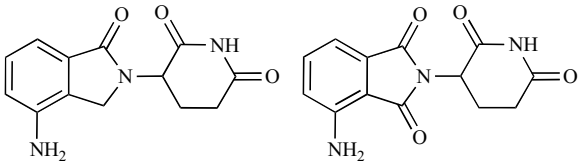
| | | | |
|---|---|---|---|
| **8** | 5-hydroxythalidomide | **11** | cis, trans-5'-hydroxy-N-(o-carboxybenzoyl)glutamic acid imide |
| **9** | cis, trans-5'-hydroxythalidomide | **12** | cis, trans-5,5'-dihydroxythalidomide |
| **10** | Thalidomide-5-O-glucuronide | **13** | 5,6-dihydroxythalidomide |

on the monohydroxylated metabolites, Table **2**, which include 5-hydroxythalidomide (5-OH) **8** formed by hydroxylation of the phthalimide ring (possibly *via* an arene oxide intermediate [19]) and 5'-hydroxythalidomide (5'-OH) **9** formed by hydroxylation of the glutarimide ring. Studies using rat liver microsomes have shown that this biotransformation is stereo-selective, with S-(-)-thalidomide preferentially forming 5-OH, and R-(+)-thalidomide preferentially forming trans-5' hydroxythalidomide, which epimerizes spontaneously to give the more stable cis isomer [20-22]. Several other metabolites have been proposed, including dihydroxylated metabolites, and a glucuronide conjugate of thalidomide was recently identified in mouse urine [23].

As previously reported the metabolic fate of thalidomide in humans is complex and poorly understood, but it is believed to involve a number of hydroxylation reactions. The end-product of metabolism, phtalic acid, is excreted as a glycine conjugate. Conjugation reactions, such as the formation of glucuronides of biologically active substances, are classically considered as detoxification processes, but metabolites can become even more active by the formation of conjugates [24]. Therefore, carbon oxidation (4-hydroxylation), N-acetylation and conjugative reactions, including glycine and glucuronide conjugation, are potentially crucial to thalidomide's metabolism and, possibly, CIPN development.

## IMMUNOMODULATORY DRUGS: IMiDs

Newer classes of α-phthalimidoglutarimides, designed and synthetized by Celgene Corp., are designated as IMiDs™ (Immunomodulatory Drugs). Their structures are shown as compound **20**, lenalidomide (CC-5013, Lenalidomide®) and compound **21**, CC-4047 (Pomalidomide, Actimid®), Fig. (**4**) and they exhibit distinct antiangiogenic activity *in vitro* in cell proliferation assays. The compounds are structural analogues of both thalidomide and the deoxy analogue EM-12, Fig. (**5**), and possess significant activity as immunomodulators [25].




**20** **21**

**Fig. (4).** Structure of IMiDs CC-5013 (lenalidomide) and CC-4047 (pomalidomide). The thalidomide structure **1** was modified by adding an amino (NH -) group at the 4 position of the pthaloyl ring to generate the IMiDs[2] CC-5013, **20**, and CC-4047, **21**. For CC-5013, one of the carbonyls (C=O) of the 4-amino-substituted phthaloyl ring has been removed.

IMiDs showed marked increases in interleukin (IL)-2 and interferon-gamma secretion. These compounds upregulate the CD40L expression on anti-CD3 stimulated T cells, resulting in activation of natural killer cells, and thus improve host immunity against tumour cells. IMiDs do not inhibit phosphosdiesterase type 4 (PDE4), a phosphodiesterase isoenzyme found in human myeloid and lymphoid lineage cells [26] that functions to maintain cAMP at low intracellular levels, resulting in modulation of LPS-induced cytokines [25]. In 2005 lenalidomide was FDA-approved for the treatment of myelodysplastic syndrome (MDS) in patients with deletion 5q cytogenetic abnormality [27] and in 2006 for use in combination with dexamethasone in patients with relapsed MM. Pomalidomide is currently in clinical development for the treatment of haematological malignancies [28-31].

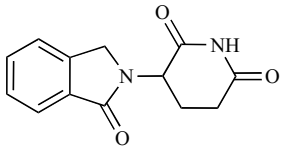



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**Fig. (5).** Structure of EM-12.

## CLINICAL EXPERIENCE WITH LENALIDOMIDE AND PERIPHERAL NEUROPATHY

### Multiple Myeloma

#### *Lenalidomide Monotherapy*

An open-label randomized phase II study in 102 heavily pre-treated, relapsed or refractory MM patients evaluated the efficacy and safety of two lenalidomide dosing regimens, 15 mg twice daily (n=35) and 30 mg once daily (n=67) on days 1-21 of a 28 day cycle [32]. Overall response rates for the once daily dose group was 24% with 4 patients (6%) achieving a complete remission, 8 (12%) having a partial remission, 4 (6%) demonstrating minor responses and 29 (43%) maintaining stable disease status. In the twice daily dose group an overall response was seen in 10 patients (29%), with 5 patients (14%) achieving partial remissions, 5 (14%) exhibiting minor responses, and 14 patients (40%) showing stable disease. Common grade 3/4 toxicities in both arms included: neutropenia (range 61-69%), leucopoenia (34-37%), lymphopenia (37-40%), thrombocytopenia (31-43%) and anaemia (14-16%). Of importance, the incidence of treatment-emergent peripheral neuropathy was 8 (23%) of 35 in the twice-daily arm versus 7 (10%) of 67 for the once-daily arm, with 3% grade 3 neuropathy.

The median number of prior lines of therapy was 4 (range, 1-13), and 56% of patients had received more than 3

lines of prior therapy. Moreover, 61%, 76%, and 18% of patients had received prior high dose chemotherapy followed by stem cell transplantation, thalidomide - prior thalidomide was permitted, but patients had to be off treatment for at least 21 days -, and bortezomib, respectively.

### *Lenalidomide Plus Dexamethasone*

The use of lenalidomide plus dexamethasone for relapsed or refractory MM was investigated in two phase III randomized, multicenter, multinational, double-blind, placebo-controlled studies comparing lenalidomide plus oral pulse high-dose dexamethasone therapy to dexamethasone therapy alone, in patients with MM who had received at least one prior treatment [33, 34]. The trials were conducted in North America (MM-009 with 353 pts) and Europe/Australia/Israel (MM-010 with 351 pts). Baseline demographic and disease-related characteristics were comparable between the lenalidomide/dexamethasone and placebo/dexamethasone groups. The patients in the two studies were not refractory to high-dose dexamethasone. In both studies, patients in the lenalidomide/dexamethasone group received 25 mg of lenalidomide once daily orally on Days 1 to 21 and a matching placebo capsule once daily on Days 22 to 28 of each 28-day cycle. Patients in the placebo/dexamethasone group received 1 placebo capsule on Days 1 to 28 of each 28-day cycle. Patients in both treatment groups took 40 mg of oral dexamethasone once daily on Days 1 to 4, 9 to 12 and 17 to 20 of each 28-day cycle for the first 4 cycles of therapy. The dose of dexamethasone was reduced to 40 mg once daily on days 1 to 4 of each 28-day cycle after the first 4 cycles of therapy. In both studies, treatment was continued until disease progression or unacceptable toxicity. Grade 3-4 adverse events were more frequent in patients who received the combination lenalidomide/dexamethasone compared to placebo/dexamethasone in both the North American and Europe/Australia/Israel studies [33, 34]. In the North American study, grade 3-4 hematologic toxicities (lenalidomide/dexamethasone *vs*. placebo/dexamethasone) were neutropenia, observed in 41.2% *vs*. 4.5% and thrombocytopenia, in 14.7% *vs*. 6.9%. A similar trend was reported in the Europe/Australia/Israel study, where the incidences of grade 3-4 neutropenia and thrombocytopenia in the lenalidomide/dexamethasone arm compared to the placebo/dexamethasone arm were 29.5% *vs*. 2.3% and 11.4% *vs*. 5.7% respectively [33]. In the lenalidomide/dexamethasone groups the incidence of grade 3-4 peripheral neuropathy was 1.7% *vs*. 1.1% in the placebo/dexamethasone arm for the North American study and 6.9% in the both arms in Europe/Australia/Israel study, generally indicated as neurological disorders, with only 0.6% of paresthesias in lenalidomide/dexamethasone group [33, 34].

In an Expanded Access Program (EAP) for lenalidomide and dexamethasone in North America more than 1400 patients with MM who received at least 1 prior therapy were studied for the likelihood of benefit and to obtain additional safety data [35]. A data snapshot of 746 patients revealed 422 patients with at least one adverse event submitted for safety analysis. The most common grade 3 adverse events were neutropenia (11.6%), anaemia (6.2%), fatigue (5.5%), thrombocytopenia (4.5%) and pneumonia (4.5%). Grade 3 neuropathy was reported in 10 patients (2.4%). Overall, of 422 patients studied, grade 1-4 neuropathy was reported in 53 patients (12.6%) [35]. Remarkably, the 67.3% of the patients in the EAP had a pre-existing neuropathy at the inclusion in the study *vs*. 28.2% of patients at the inclusion in the North American study [33].

In a phase II study, 34 newly diagnosed MM patients were treated with lenalidomide 25 mg on days 1-21 of a 28-day cycle and dexamethasone [36]. After four cycles of treatment, patients were allowed to proceed to stem cell transplant (SCT) or remain on treatment with dexamethasone reduced from 40 mg, days 1-4, 9-12, and 17-20, to 40 mg days 1-4 of each cycle. Ninety-one percent reported an objective response, with a median time to response of one month. Six patients (18%) achieved a complete response and 13 (38%) achieved a "very good partial response". In addition, 35% of patients exhibited a partial response. Among the 21 patients who elected to continue in the study rather than proceed to SCT and received a median of 19 cycles of therapy, 24% achieved complete response, 43% had a very good partial response and 19% a partial response. For the entire cohort, 2-year time to progression (TTP) rate was 71% and 3-year overall survival (OS) was 88%. Grade 3 or higher non-haematological toxicities were seen in 55% of patients [37]. The most common adverse events grade ≥3 were neutropenia (21%), leucopoenia (9%), lymphopenia (6%), anaemia (6%), fatigue (21%), muscle weakness (6%), anxiety (6%), pneumonitis (6%) and rash (6%) [36]. The three most common grade 1-2 adverse events were fatigue (41%), muscle weakness (29%), and neuropathy (21%). In the phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed patients with MM coordinated by the Eastern Cooperative Oncology Group (E4A03), peripheral neuropathy was reported in 2% of the patients in high-dose arm compared with 1.5% in the low dose arm [38].

### *Lenalidomide, Bortezomib and Dexamethasone*

A retrospective review of 17 naive patients with MM treated with bortezomib-lenalidomide-dexamethasone reported disease remission in 14 patients (82%) including 2 patients (12%) with complete response. Adverse events included deep venous thrombosis (1 patient), short term grade 3 neuropathy (1 patient), grade 3 thrombocytopenia (1 patient) and non-neutropenic pneumonia (1 patient) [39].

In a single-centre study, 78 patients with recurrent MM who had received bortezomib were retrospectively reviewed for the incidence, severity and risk factors for peripheral neuropathy [40]. Before bortezomib treatment 29 patients (37%) reported grade 1 or 2 neuropathy and 1 patient had grade 3. Seventeen patients (22%) had diabetes mellitus and 66 patients (85%) had received prior thalidomide, both factors which may contribute to peripheral neuropathy [40]. In 6 of 9 patients who experienced peripheral neuropathy with bortezomib, two weeks after switching treatment to lenalidomide, significant unexpected improvement in peripheral neuropathy symptoms was observed, including 3 patients who were able to stop analgesics, although a clear causal relationship between lenalidomide treatment and neuropathy course could not be established.

### Myelodysplastic Syndromes

One of the adverse events reported in clinical studies of patients with deletion 5q MDS treated with lenalidomide was peripheral neuropathy (overall 5.4%) [41]. No cases of peripheral neuropathy were reported in the MDS-003 registration trial in patients with transfusion-dependent anaemia due to low/intermediate-1 risk MDS with deletion 5q cytogenetic abnormality with or without other cytogenetic abnormalities [42]. In additional trials (MDS-001 and MDS-002) no cases of peripheral neuropathy were reported [43, 44].

### Recurrent Epithelial Ovarian Cancer

Lenalidomide was evaluated in a phase I/II study in patients with recurrent epithelial ovarian cancer following platinum and taxane based combination therapy and at least one second-line therapy [45]. Of the 15 patients averaging 3 prior chemotherapies in the study peripheral neuropathy (grade 1-2) was observed in 4 (27%) patients.

## LENALIDOMIDE AND PERIPHERAL NEUROPATHY (POSTMARKETING DATA)

As usual with any new drug, important information on the actual toxicity profile in daily clinical practice can be obtained only from the postmarketing surveillance data, available for lenalidomide from the Celgene archives.

The MedDRA version 10.1 Standardized MedDRA Query (SMQ) for peripheral neuropathy with the Preferred Terms categorized as narrow scope was used to retrieve the cases from the drug safety database. Selected Preferred Terms such as Dysesthesia, Hypoesthesia, and Paresthesia that are categorized as broad scope were considered neuropathy and were also used to retrieve cases from the drug safety database. The Preferred Terms (PT) that were retrieved are shown in Table **3**; all the events will be collectively referred to as neuropathy for the purpose of this review. All the events of neuropathy, which were included in this database, were reported by health care professionals and assessed either by the reporter or by Celgene as suspected to be related to lenalidomide. The period covered was December 27th, 2005 to December 27th, 2007. It's very important to be fully aware that these are spontaneous notifications and that they are consistently affected by under-reporting because of their own nature. We cannot measure the real incidence of CIPN from these data but they can be useful to monitor and trace eventual safety signals.

During the covered period, a total of 28,625 patients were dispensed lenalidomide for various indications (18,693 for MM 7,764 for MDS, and 2,168 for other indications) in the commercial environment in United States. An estimated 7,383 patients were dispensed lenalidomide in Europe, of

**Table 3. Number and Reporting Rate (%) of Neuropathy by Indication and Source**

| Preferred Term | Postmarketing (US) | | | Postmarketing (Europe) | | Total |
|---|---|---|---|---|---|---|
| | MM n (RR %) | MDS n (RR %) | Other[1] n (RR %) | MM n (RR %) | Other[2] n (RR %) | |
| Demyelinating polyneuropathy | 0 | 1 (0.01) | 0 | 0 | 0 | 1 |
| Dysesthesia | 1 (0.01) | 0 | 0 | 0 | 0 | 1 |
| Hypoesthesia | 23 (0.12) | 2 (0.03) | 4 (0.18) | 0 | 0 | 29 |
| Neuralgia | 1 (0.01) | 0 | 0 | 0 | 0 | 1 |
| Neuritis | 0 | 1 (0.01) | 0 | 0 | 0 | 1 |
| Neuropathy | 41 (0.22) | 8 (0.10) | 3 (0.14) | 3 (0.05) | 2 (0.16) | 57 |
| Neuropathy peripheral | 17 (0.09) | 1 (0.01) | 1 (0.05) | 0 | 0 | 19 |
| Paresthesia | 11 (0.06) | 2 (0.03) | 3 (0.14) | 1 (0.02) | 1 (0.08) | 18 |
| Peripheral motor neuropathy | 0 | 0 | 1 (0.05) | 0 | 0 | 1 |
| Peripheral sensory neuropathy | 1 (0.01) | 0 | 1 (0.05) | 0 | 0 | 2 |
| Polyneuropathy | 0 | 0 | 0 | 1 (0.02) | 1 (0.08) | 2 |
| Sensory loss | 1 (0.01) | 0 | 0 | 0 | 0 | 1 |
| Total | 96 (0.51) | 15 (0.19) | 13 (0.60) | 5 (0.08) | 4 (0.32) | 133 (0.37) |

MM = multiple myeloma; MDS = myelodisplastic syndrome; RR = reporting rate

[1] Other indications include ovarian cancer metastatic (1), chronic lymphocytic leukemia (1), amyloidosis (2), prostate cancer (1), myelofibrosis (1), lymphoproliferative disorder (1), and unknown (3).

[2] Other indications were unspecified.

which about 83% (6,114) had MM and about 17% (1,269) had unspecified other indications. The number of reports and reporting rate of neuropathy by indication and source is found in Table **3**.

### Multiple Myeloma

Out of an estimate of 18,693 patients prescribed with lenalidomide for MM, during the covered period a total of 96 events of neuropathy were reported by 87 patients. Nine of them had more than one event (hypoesthesia and paresthesia). The median age of the 87 patients was 68 years (range: 38-89 years). Sixty-one percent (61%) of the patients were over 65-year-old. There were 39 females, 49 males, and 4 of unknown gender and 73% (70/96) of the events of neuropathy were considered to be non-serious. The median time to onset of the neuropathy for 33 reports with available information was 60 days (range: 4-1825). For the outcome of the events with available information, 16 patients recovered, 22 patients had not recovered at the time of the report, and recovery status was unknown/not provided in 58 reports. Of the 35 reports with available information, relevant medical history and/or concurrent conditions that could have contributed to the neuropathy were pre-existing neuropathy, diabetes, hypothyroidism, renal failure, and alcohol use.

### Myelodysplastic Syndrome

Out of an estimate of 7764 patients with MDS being prescribed with lenalidomide, a total of 15 events of neuropathy were reported by 14 MDS patients during the postmarketing period covered. The median age of MDS patients was 71.5 years (range: 37-89). Ten of the 14 patients were over 65-year-old. There were 9 females and 5 males and 80% (12/15) of the events of neuropathy were considered to be non-serious. The median time to onset of neuropathy for 7 reports with available information was 30 days (range: 28-180). Two patients recovered in the follow-up, 4 did not recover and the outcome was unknown/not provided in 9 reports. Of the 7 reports with available information, relevant medical history and/or concurrent conditions that could have contributed to the neuropathy were pre-existing neuropathy, rheumatoid arthritis, vitamin B12 deficiency, hepatic cirrhosis, hypothyroidism, and tobacco use.

### Other Indications

Out of an estimate of 2168 patients who received lenalidomide for other indications than MM and MDS a total of 13 events of neuropathy were reported by 10 patients during the covered period. Three of the 10 patients had more than one event, of which 2 patients had hypoesthesia and paresthesia, and one patient had paresthesia and peripheral motor neuropathy. The median age of the patients was 76 years (range: 41-78). Four of the 7 patients with available information were over 65-year-old. There were 6 males, 1 female, and 3 of unknown gender and 77% (10/13) of the events of neuropathy were considered to be non-serious. The median time to onset of neuropathy for 6 reports with available information was 49 days (range: 34-117). Three patients recovered in the follow-up, 1 has not recovered at the time of the report, and the outcome was unknown/not provided in 9 reports. Of the 2 reports with available information, relevant medical history that could have contributed to the neuropathy was pre-existing neuropathy.

## POMALIDOMIDE

Pomalidomide (CC-4047) is a co-stimulatory thalidomide analogue that can prime protective, long-lasting, tumour specific, Th1-type responses *in vivo* [46].

A phase I study using the drug evaluated 24 relapsed or refractory MM patients that were treated with a dose-escalating regimen of oral pomalidomide [47]. Pomalidomide treatment was associated with significantly increased serum IL-2 receptor and IL-12 levels, which is consistent with activation of T cells and monocytes and macrophages. Clinical activity was noted in 67% of patients with greater than 25% reduction in paraprotein, but, interestingly, 13 patients experienced a greater than 50% reduction in paraprotein, and four (17%) of 24 patients entered complete remission. The treatment-related thrombosis incidence was 12.5%, similar to treatment with thalidomide alone in MM [48]. Similar to lenalidomide, the dose-limiting toxicity was myelosuppression, with neutropenia occurring in 6 patients within 3 weeks of starting therapy.

Recently, a Phase 1 study to determine the maximum tolerated dose (MTD) of pomalidomide at 1 mg, 2 mg, 5 mg and 10 mg on alternate days was performed [49]. Twenty patients with relapsed myeloma were treated. Grade 4 neutropenia occurred in all patients receiving 10 mg and the MTD was defined as 5 mg on alternate days. No thrombotic events were observed. Notably, neurological complications were limited to transient tremor in 2/20 patients and there was no reported somnolence. Pomalidomide was continued following the 4-week MTD study in 17/20 patients for a median of 14 months and 10% of patients had a complete response, while >50% reduction in paraprotein was achieved in 50% of subjects. Progression-free survival was 10.5 months and median overall survival was 33 months. A significant rise was observed in the proportion of CD8+ cells. Alternate day pomalidomide was associated with a marked reduction in the incidence of thrombosis whilst maintaining excellent anti-myeloma activity

Based on the different activity profile of this agent, as compared to lenalidomide, plans are in place to advance this compound into Phase II trials to further evaluate its efficacy and safety profile in several hematologic malignancies and solid tumours [50].

## CONCLUSION

The IMiDs model is an interesting example of the possibility to "tailor" the pharmacologic properties of new molecules starting from an active, but potentially markedly toxic, first-in-class molecule.

This attempt is even more important in the case of IMiDs since thalidomide is a peculiar molecule with an extremely complex, specie-specific metabolism, a feature that enhance the difficulty of researchers when they try to dissect out the "positive effects" from the undesired side effect of the drug.

The results obtained so far with lenalidomide, and to a lesser extent with pomalidomide, in terms of reduced inci-

dence of neurotoxic effects are very promising and, if they will be confirmed by further experimental data and clinical practice, they will represent one of the most valid result of pharmacological research recently reported in the field of antineoplastic chemotherapy.

## REFERENCES


[1] Sampaio, E.P.; Kaplan, G.; Miranda, A.; Nery, J.A.; Miguel, C.P.; Viana, S.M.; Sarno, E.N. The influence of thalidomide on the clinical and immunologic manifestation of erythema nodosum leprosum. *J. Infect. Dis*., **1993**, *168*, 408 - 14.

[2] http://www.cancer.gov/cancertopics/druginfo/fda-thalidomide

[3] Zeldis, J.B.; Williams, B.A.; Thomas, S.D.; Elsayed, M.E. S.T.E.P.S.: a comprehensive program for controlling and monitoring access to thalidomide. *Clin. Ther.*, **1999**, *21*, 319 - 30.

[4] Isoardo, G.; Bergui, M.; Durelli, L.; Barbero, P.; Boccadoro, M.; Bertola, A.; Ciaramitaro, P.; Palumbo, A.; Bergamasco, B.; Cocito, D. Thalidomide neuropathy: clinical, electrophysiological and neuroradiological features. *Acta Neurol. Scand.*, **2004**, *109*, 188 - 93.

[5] Giannini, F.; Volpi, N.; Rossi, S.; Passero, S.; Fimiani, M.; Cerase, A.. Thalidomide-induced neuropathy: a ganglionopathy? *Neurology*, **2003**, *60*, 877 - 78.

[6] Steurer, M.; Spizzo, G.; Mitterer, M.; Gastl, G. Low-dose thalidomide for multiple myeloma: interim analysis of a compassionate use program. *Onkologie*, **2004**, *27*, 150 - 64.

[7] Cavaletti, G.; Beronio, A.; Reni, L.; Ghiglione, E.; Schenone, A.; Briani, C.; Zara, G.; Cocito, D.; Isoardo, G.; Ciaramitaro, P.; Plasmati, R.; Pastorelli, F.; Frigo, M.; Piatti, M.; Carpo, M.. Thalidomide sensory neurotoxicity: a clinical and neurophysiologic study. *Neurology*, **2004**, *62*, 2291-93.

[8] Briani, C.; Zara, G.; Rondinone, R.; Della Libera, S.; Ermani, M.; Ruggero, S.; Ghirardello, A.; Zampieri, S.; Doria, A. Thalidomide neurotoxicity: prospective study in patients with lupus erythematosus. *Neurology*, **2004**, *62*, 2288 - 90.

[9] Tosi, P.; Zamagni, E.; Cellini, C.; Plasmati, R.; Cangini, D.; Tacchetti, P.; Perrone, G.; Pastorelli, F; Tura, S.; Baccarani, M.; Cavo, M. Neurological toxicity of long-term (>1 yr) thalidomide therapy in patients with multiple myeloma. *Eur. J. Haematol.*, **2005**, *74*, 212 - 16.

[10] Bastuji-Garin, S.; Ochonisky, S.; Bouche, P.; Gherardi, R.K.; Duguet, C.; Djerradine, Z.; Poli, F.; Revuz, J. Incidence and risk factors for thalidomide neuropathy: a prospective study of 135 dermatologic patients. *J. Invest. Dermatol.*, **2002**, *119*, 1020 - 26.

[11] Williams, R.T.; Parke, D.V. Metabolic fate of drugs. *Ann. Rev. Pharmacol.*, **1964**, *4*, 85 - 114.

[12] Lepper, E.R.; Smith, N.F.; Cox, M.C.; Scripture, C.D.; Figg, W.D. Thalidomide metabolism and hydrolysis: mechanisms and implications. *Curr. Drug Metab.*, **2006**, *6*, 677 - 85.

[13] Chung, F.; Lu, J.; Palmer, B.D.; Kestell, P.; Browett, P.; Baguley, B.C.; Tingle, M.; Ching, L.M. Thalidomide pharmacokinetics and metabolite formation in mice, rabbits, and multiple myeloma patients. *Clin. Cancer Res.*, **2004**, *10*(17), 5949 - 56.

[14] Beckmann, R. The behavior of thalidomide in the human and animal organism. Part 2. *Arzneimittel-Forschung*, **1963**, *13*, 185 -91.

[15] Jonsson, N. A. Chemical structure and teratogenic properties.3. Review of available data on structure-activity relationships and mechanism of action of thalidomide analogs. *Acta Pharm. Suec.*, **1972**, *9*(6), 521 - 42.

[16] Keberle, H.; Faigle, J.W.; Fritz, H.; Knusel, F.; Loustalot, P.; Schmid, K. Embryopathic Activity of Drugs. Churchill: London, **1965**.

[17] Schumacher, H.; Smith, R.L.; Williams, R.T. Metabolism of thalidomide - Spontaneous hydrolysis of thalidomide in solution. *Br. J. Pharmacol. Chem.*, **1965**, *25*(2), 324 - 37.

[18] Williams, R.T.; Schumacher, H.; Fabro, S.; Smith, R.L. Embryopathic Activity of Drugs. Churchill: London, **1965**.

[19] Gordon, G.B.; Spielberg, S.P.; Blake, D.A.; Balasubramanian, V. Thalidomide teratogenesis: evidence for a toxic arene oxide metabolite. *Proc. Natl. Acad. Sci. USA*, **1981**, *78*(4), 2545 - 48.

[20] Weinz, C. and Blaschke, G. Investigation of the *in vitro* biotransformation and simultaneous enantioselective separation of thalidomide and its neutral metabolites by capillary electrophoresis. *J. Chromatogr. B. Biomed. Appl.*, **1995**, *674*(2), 287 - 92.

[21] Meyring, M.; Muhlbacher, J.; Messer, K.; Kastner-Pustet, N.; Bringmann, G.; Mannschreck, A.; Blaschke, G. *In vitro* biotransformation of (R)- and (S)-thalidomide: application of circular dichroism spectroscopy to the stereochemical characterization of the hydroxylated metabolites. *Anal. Chem.*, **2002**, *74(15)*, 3726 - 35.

[22] Meyring, M.; Muhlenbrock, C.; Blaschke, G. Investigation of the stereoselective *in vitro* biotransformation of thalidomide using a dual cyclodextrin system in capillary electrophoresis. *Electrophoresis*, **2000**, *21*(15), 3270 - 79.

[23] Lu, J.; Palmer, B.D.; Kestell, P.; Browett, P.; Baguley, B.C.; Muller, G.; Ching, L.M. Thalidomide metabolites in mice and patients with multiple myeloma. *Clin. Cancer Res.*, **2003**, *9(5)*, 1680 - 88.

[24] Olson, J.A.; Moon, R.C.; Anders, M.W.; Fenselau, C.; Shane, B. Enhancement of biological activity by conjugation reactions. *J. Nutr.*, **1992**, *122* (3 Suppl), 615 - 24.

[25] 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 inhlbitors of TNF-alpha production. *Bioorg. Med. Chem. Lett.*, **1999**, *9(11)*, 1625 - 30.

[26] Verghese, M.W.; McConnell, R.T.; Lenhard, J.M.; Hamacher, L.; Jin, S.L. Regulation of distinct cyclic AMP-specific phosphodiesterase (phosphodiesterase type 4) isozymes in human monocytic cells. *Mol Pharmacol.*, **1995**, *47*, 1164 - 71.

[27] New treatment for myelodysplastic syndrome. *FDA Consum. Mag.*, **2006**, *40*(2).

[28] Hernandez-Ilizaliturri, F.J.; Reddy, N.; Holkova, B.; Ottman, E.; Czuczman, M.S. Immunomodulatory drug CC-5013 or CC-4047 and rituximab enhance antitumor activity in a severe combined immunodeficient mouse lymphoma model. *Clin. Cancer. Res.*, **2005**, *11*, 5984 - 92.

[29] Schey, S.A.; Fields, P.; Bartlett, J.B.; Clarke, I.A.; Ashan, G.; Knight, R.D.; Streetly, M.; Dalgleish, A.G. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J. Clin. Oncol.*, **2004**, *22*, 3269 - 76.

[30] Davies, F.E.; Raje, N.; Hideshima, T.; Lentzsch, S.; Young, G.; Tai, Y.T.; Lin, B.; Podar, K.; Gupta, D.; Chauhan, D.; Treon, S.P.; Richardson, P.G.; Schlossman, R.L.; Morgan, G.J.; Muller, G.W.; Stirling, D.I.; Anderson, K.C. Thalidomide and immunomodulatory derivatives augment natural killer cell cytotoxicity in multiple myeloma. *Blood*, **2001**, *98*, 210 - 16.

[31] Koh, K.R.; Janz, M.; Mapara, M.Y.; Lemke, B.; Stirling, D.I.; Dorken, B.; Zenke, M.; Lentzsch, S. Immunomodulatory derivative of thalidomide (IMiD CC-4047) induces a shift in lineage commitment by suppressing erythropoiesis and promoting myelopoiesis. *Blood*, **2005**, *105*, 3833 - 40.

[32] Richardson, P.G.; Blood, E.; Mitsiades, C.S.; Jagannath, S.; Zeldenrust, S.; Alsina, M.; Schlossman, R.L.; Rajkumar, S.V.; Desikan, K.R.; Hideshima, T.; Munshi, N.; Kelly-Colson, K.; Doss, D.; McKenney, M.; Gorelik, S.; Warren, D.; Freeman, A.; Rich, R.; Wu, A.; Olesnyckyj, M.; Wride, K.; Dalton, W.; Zeldis, J.; Knight, R.; Weller, E.; Anderson, K.C. A randomized phase 2 study of lenalidomide therapy for patients with relapsed or relapsed and refractory multiple myeloma. *Blood*, **2006**, *108*(10), 3458 - 64.

[33] Dimopoulos, M.; Spencer, A.; Attal, M.; Prince, H.M.; Harousseau, J.L.; Dmoszynska, A.; San Miguel, J.; Hellmann, A.; Facon, T.; Foa, R.; Corso, A.; Masliak, Z.; Olesnyckyj, M.; Yu, Z.; Patin, J.; Zeldis, J.B.; Knight, R.D. Lenalidomide plus dexamethasone for relapsed or refractory multiple myeloma. *N. Eng. J. Med.*, **2007**, *357*(21), 2123 - 32.

[34] Weber, D.M.; Chen, C.; Niesvizky, R.; Wang, M.; Belch, A.; Stadtmauer, E.A.; Siegel, D.; Borrello, I.; Rajkumar, S.V.; Chanan-Khan, A.A.; Lonial, S.; Yu, Z.; Patin, J.; Olesnyckyj, M.; Zeldis, J.B.; Knight, R.D. Lenalidomide plus dexamethasone for relapsed multiple myeloma in North America. *N. Eng. J. Med.*, **2007**, *357*(21), 2133 - 42.

[35] Chen, C.; Reece, D.E.; Siegel, D.; Niesvizky, R.; Boccia, R.V.; Stadtmauer, E.E.A.; Abonour, R.; Irwin, D.; Polikoff, J.; Kumar, S.; Gams, R.A.; Kenvin, L.; McElveen, D.; Hu, A.; Pietronigro, D.; Knight, R.D.; Zeldis, J.B. Expanded access program (EAP) for lenalidomide (Revlimid) plus dexamethasone in over 1400 subjects with relapsed or refractory multiple myeloma [abstract]. *Blood: ASH Annual Meeting Proceedings*; *108*(11 Part 1 of 2): 1015a-6a, Abstract # 3556, **2006**.

[36] Rajkumar, S.V.; Hayman, S.R.; Lacy, M.Q.; Dispenzieri, A.; Geyer, S.M.; Kabat, B.; Zeldenrust, S.R.; Kumar, S.; Greipp, P.R.;

Fonseca, R.; Lust, J.A.; Russell, S.J.; Kyle, R.A.; Witzig, T.E.; Gertz, M.A. Combination therapy with lenalidomide plus dexamethasone (Rev/Dex) for newly diagnosed myeloma. *Blood*, **2005**, *106(13)*, 4050 - 53.

[37] Lacy, M.Q.; Gertz, M.A.; Dispenzieri, A.; Hayman, S.R.; Geyer, S.; Kabat, B.; Zeldenrust, S.R.; Kumar, S.; Greipp, P.R.; Fonseca, R.; Lust, J.A.; Russell, S.J.; Kyle, R.A.; Witzig, T.E.; Bergsagel, P.L.; Stewart, A.K.; Rajkumar, S.V. Long-term results of response to therapy, time to progression, and survival with lenalidomide plus dexamethasone in newly diagnosed myeloma. *Mayo Clin. Proc.*, **2007**, *82*(10), 1179 - 84.

[38] Rajkumar, S.V.; Jacobus, S.; Callander, N.; Fonseca, R.; Vesole, D.; Williams, M.; Abonour, R.; Siegel, D.; Greipp, P. Phase III trial of lenalidomide plus high-dose dexamethasone versus lenalidomide plus low-dose dexamethasone in newly diagnosed multiple myeloma (E4A03): A trial coordinated by the Eastern Cooperative Oncology Group [slides]. *Oral presented at: the 49th Annual Meeting of the American Society of Hematology 2007*; December 8-11, Atlanta, GA, **2007**.

[39] Wang, M.; Delasalle, K.; Giralt, S.; Alexanian, R. Rapid control of previously untreated multiple myeloma with bortezomib-lenalidomide-dexamethasone (BLD) [abstract]. *Blood: ASH Annual Meeting Proceedings*; *110*(11, Part 1 of 2): 1057A, Abstract #3611, **2007**.

[40] Badros, A.; Goloubeva, O.; Dalal, J.S.; Can, I.; Thompson, J.; Rapoport, A.P.; Heyman, M.; Akpek, G.; Fenton, R.G. Neurotoxicity of bortezomib therapy in multiple myeloma: A single-center experience and review of the literature. *Cancer*, **2007**, *110(5)*, 1042 - 49.

[41] Celgene Corporation Data On File **2007**.

[42] List, A.; Dewald, G.; Bennett, J.; Giagounidis, A.; Raza, A.; Feldman, E.; Powell, B.; Greenberg, P.; Thomas, D.; Stone, R.; Reeder, C.; Wride, K.; Patin, J.; Schmidt, M.; Zeldis, J.; Knight, R. Lenalidomide in the myelodysplastic syndrome with chromosome 5q deletion. *N. Eng. J. Med.*, **2006**, *355*(14), 1456 - 65.

[43] List, A.F.; Kurtin, S.; Roe, D.J.; Buresh, A.; Mahadevan, D.; Fuchs, D.; Rimsza, L.; Heaton, R.; Knight, R.; Zeldis, J.B. Efficacy of lenalidomide in myelodysplastic syndromes. *N. Eng. J. Med.*, **2005**, *352*(6), 549 - 57.

[44] Raza, A.; Reeves, J.A.; Feldman, E.J.; Dewald, G.W.; Bennett, J.M.; Deeg, H.J.; Dreisbach, L.; Schiffer, C.A.; Stone, R.M.; Greenberg, P.L.; Curtin, P.L.; Klimek, V.M.; Shammo, J.M.; Thomas, D.; Knight, R.D.; Schmidt, M.; Wride, K.; Zeldis, J.B.; List, A.F. Phase II study of lenalidomide in transfusion-dependent, low- and intermediate-1-risk myelodysplastic syndromes with karyotypes other than deletion 5q. *Blood*, **2008**, *111*(1), 86 - 93.

[45] Teng, N.H.; Husain, A.; Chan, J.K.; Donohue, T.R. A novel immunomodulatory agent Lenalidomide (Revlimid®) in recurrent Epithelial Ovarian Cancer (EOC). *Western Assoc. Gynecol. Oncol.* **2005**; Abstract #5103.

[46] Dredge, K.; Marriott, J.B.; Todryk, S.M.; Muller, G.W.; Chen, R.; Stirling, D.I.; Dalgleish, A.G. Protective antitumor immunity induced by a costimulatory thalidomide analog in conjunction with whole tumor cell vaccination is mediated by increased Th1-type immunity. *J. Immunol.*, **2002**, *168(10)*, 4914 - 19.

[47] Schey, S.A.; Fields, P.; Bartlett, J.B.; Clarke, I.A.; Ashan, G.; Knight, R.D.; Streetly, M.; Dalgleish, A.G. Phase I study of an immunomodulatory thalidomide analog, CC-4047, in relapsed or refractory multiple myeloma. *J. Clin. Oncol.*, **2004**, *22(16)*, 3269 - 76.

[48] Urbauer E, Kaufmann H, Nösslinger T, Raderer M, Drach J. Thromboembolic events during treatment with thalidomide. *Blood*, **2002**, *99*(11), 4247 - 48.

[49] Streetly MJ, Gyertson K, Daniel Y, Zeldis JB, Kazmi M, Schey SA. Alternate day pomalidomide retains anti-myeloma effect with reduced adverse events and evidence of *in vivo* immunomodulation. *Br. J. Haematol.*, **2008**, *141*(1), 41 - 51.

[50] Research IMiDs. http://www.celgene.com/research/imids-immunomudulators.aspx and http://www.celgene.com/pdfs/product_pipeline.pdf; Accessed on: October 30, **2008**.

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