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REVIEW

Therapeutic effects of thalidomide in hematologic disorders: a review

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Abstract **The extensive autoimmune, anti-inflammatory, and anticancer applications of thalidomide have inspired a growing number of studies and clinical trials. As an inexpensive agent with relatively low toxicity, thalidomide is regarded as a promising therapeutic candidate, especially for malignant diseases. We review its therapeutic effects in hematology, including those on multiple myeloma, Waldenstroem macroglobulinemia, lymphoma, mantle-cell lymphoma, myelodysplastic syndrome, hereditary hemorrhagic telangiectasia, and graft-versus-host disease. Most studies have shown satisfactory results, although several have reported the opposite. Aside from optimal outcomes, the toxicities and adverse effects of thalidomide should also be examined. The current work includes a discussion of the mechanisms through which the novel biological effects of thalidomide occur, although more studies should be devoted to this aspect. With appropriate safeguards, thalidomide may benefit patients suffering from a broad variety of disorders, particularly refractory and resistant diseases.**

Keywords thalidomide; multiple myeloma; lymphoma

Introduction

Over the years, thalidomide has gained both popularity and notoriety worldwide. It was first introduced as a non-barbiturate sedative-hypnotic drug in West Germany in the 1950s. Animal experiments showed that it has advantages over other agents because it presents fewer adverse effects and patients exhibit better tolerance to such medication. Its consumption grew rapidly in Europe and Canada. The antiemetic effect of thalidomide was also exploited as a means of alleviating morning sickness during pregnancy. In 1961, however, thalidomide was withdrawn from markets all over the world because it potentially causes teratogenesis [1]. Nevertheless, researches continued looking into the mechanism of action of thalidomide. Its indications has expanded with scientific progress since it was approved by the US Food and Drug Administration in 1997 as an agent for treating erythema nodosum leprosum. Further studies revealed that thalidomide effectively treated autoimmune diseases, such as chronic graft-versus-host disease and rheumatoid arthritis. Thalidomide has also become known as an immune-modulatory agent for autoimmune diseases, as well as a therapeutic alternative in anti-inflammatory and anticancer fields. This review presents the application of thalidomide in hematologic diseases and its potential adverse effects.

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Therapeutic application

Thalidomide in the treatment of multiple myeloma

Multiple myeloma (MM) is a malignant plasma-cell proliferative disorder that accounts for approximately 1% of all cancers and 10% of hematologic cancers; it kills more than 11 000 people each year [2]. The initial agent reported to induce remission was melphalan, but the response rate was only one-third of patients treated with this drug, an unsatisfactory result. Early therapy of combined melphalan and prednisolone (MP) improved the response rate to about 50%, but few patients achieved long-term remission. In 1998, an overview that compares combination chemotherapy with MP in 27 randomized trials showed no difference in mortality [3]. Other combinations, such as those featuring interferon alpha, slightly promoted event-free survival (EFS), but offered no improvement in overall survival (OS). For patients

for whom chemotherapy failed, only limited options for a salvage regimen were available. Research has shown that proliferative plasma cells and stromal cells can secrete adhesion cytokines that promote angiogenesis; such cytokines include LFA-1, VLA-4, LAM-1, and CD44 [4]; findings have also indicated that angiogenesis occurs with tumor growth. Further studies were conducted to confirm the extent of bone marrow angiogenesis, revealing that the proliferation of plasma cells is correlated with active MM [5]. Thalidomide has been defined as an antiangiogenic, antitumor, and immunomodulatory agent [6]. In 1965, it was first reported to slow disease progression in one case. In 1999, Singhal *et al.* were the first to reveal the beneficial effect of thalidomide after its addition to a previously implemented therapy for refractory MM [7]. Initially, combination therapy is based on the effectiveness of a single agent. With years of progress and advancements in pharmacology and drug interactions, combination therapies became more rationally designed. Thalidomide, as well as two other novel agents, bortezomib, lenalidomide, was introduced as a new regimen for a combination therapy designed to target the biological pathway of MM [8].

As a newly proposed agent in the hematologic field, thalidomide provides options for end-stage myeloma and markedly broadens the range of therapeutic applications [9]. The promising therapeutic results of thalidomide and its derivatives have also recently been validated [10].

The mechanism by which thalidomide arrests MM can be summarized as follows. First, it imposes pro-apoptotic effects, thereby arresting MM cells in the G_1 phase; second, thalidomide downregulates the binding of MM cells to bone marrow stromal cells (BMSCs)—a feature that confers cell adhesion-mediated drug resistance; and third, it inhibits growth factors, including IL-6, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF), all of which are critical in the growth and metastasis of MM cells [10–12]. VEGF concentrations were dramatically reduced by thalidomide treatment.

Thalidomide also activates the immunological system by co-stimulating primarily human T cells, as well as nature killer (NK) and NKT lymphocytes, thereby inducing their proliferation, cytokine production, and cytotoxic activity [13]. The potential molecular targets associated with MM pathogenesis have been evaluated. The results showed that the anti-myeloma activity of thalidomide is associated with the mechanism responsible for its teratogenic effect, and that the inhibition of GC-rich promoter genes is attributed mostly to *S*-racemate [14]. Succeeding studies have demonstrated that the inhibition of both tumor and vascular growth by thalidomide may be synergistic [15].

A study of 668 MM patients between 1998 and 2004 suggested that thalidomide incorporated in a high-dose therapy (HDT) with melphalan increases the response rate and extends EFS; however, the high possibility of a higher

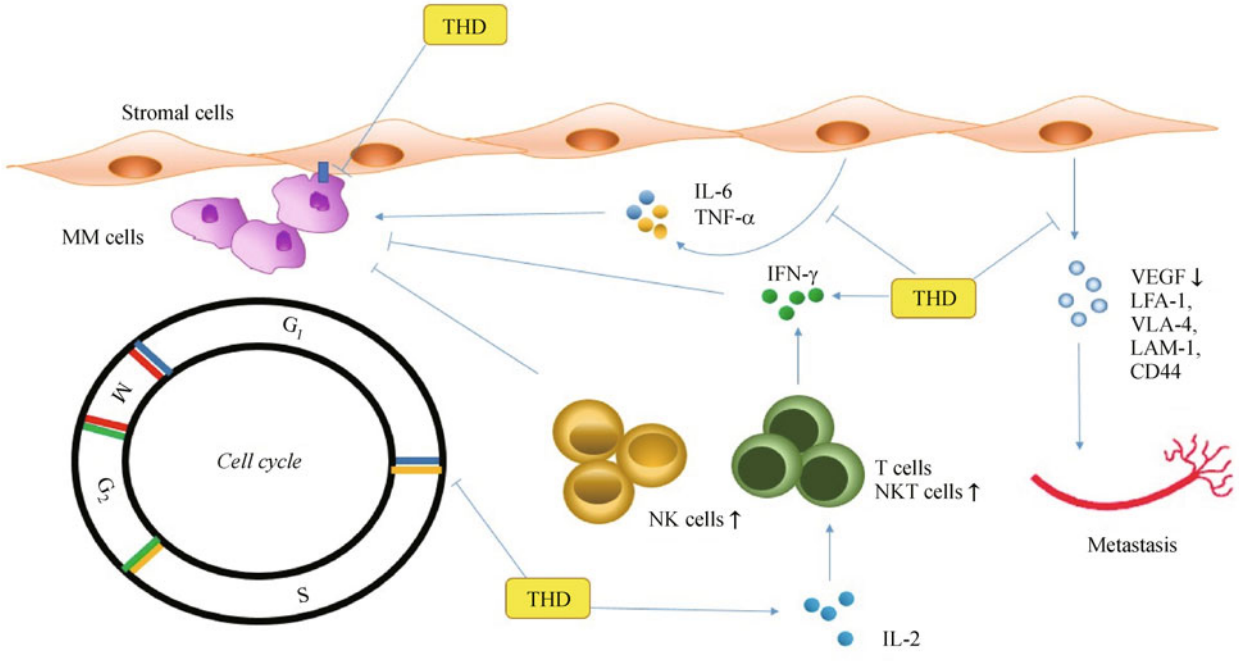

Fig. 1 Mechanism of thalidomide on MM cells. Thalidomide arrests MM cells in the G_1 phase by inhibiting the bond between stromal and MM cells. According to studies, metastasis is correlated with vascular proliferation. Thalidomide can decrease cytokine production by stromal cells, such as VEGF, thereby preventing angiogenesis. Thalidomide inhibits the production of IL-6 and TNF-β, which assists the growth of MM cells and promotes IFN-γ secretion, which leads to the apoptosis of MM cells. It also stimulates T cells and NKT cells by increasing the IL-2 level. Both T and NKT cells have cytotoxic effects on MM cells.

frequency of additional adverse effects should also be considered [16].

In a phase III clinical trial, the response rate derived with thalidomide plus dexamethasone was considerably higher than that attained with dexamethasone alone (63% vs. 41%, respectively; $P = 0.0017$), indicating that thalidomide is an indispensable agent in remedying MM. However, the incidence rate of toxicity was also higher than that observed with dexamethasone alone (grade 3 or higher deep vein thrombosis (DVT), rash, bradycardia, neuropathy, and grade 4 to 5 toxicity), particularly in the first four months of treatment. This result suggests that an ideal regimen is one that balances the efficacy and toxicity of thalidomide [17].

An intent-to-treat analysis of 333 evaluable patients showed significantly higher response rates in MP- and thalidomide (MP-T)-treated patients over those achieved in only MP-treated patients, demonstrating that thalidomide improves response rate and induces a very good partial response in elderly patients with newly diagnosed MM [18].

Another clinical trial investigated the synergy of thalidomide and dexamethasone in advanced and refractory MM as initial therapy. The combination is an effective and relatively well-tolerated induction regimen for previously untreated patients with MM. It may serve as an orally administered alternative to vincristine-doxorubicin-dexamethasone in preparation for autologous stem cell transplantation (ASCT) [19].

With the growing developments in the management of MM, HDT followed by ASCT reveals effects on both the tumor clone and bone marrow microenvironments. Compared with conventional chemotherapy results, the positive contributions of ASCT to MM treatment increase when combined with novel agents, such as thalidomide [20].

As the range of choices expands, conventional chemotherapy has been substituted by regimens characterized by the combination of thalidomide with other agents. This development has improved the depth of response, a result that is interpreted as reflective of extended progression-free survival (PFS) and, potentially, OS [21]. Thalidomide shows high activity in myeloma with minimal myelosuppression, making it a good option for induction therapy prior to HDT with ASCT [22]. A randomized trial intended to compare bortezomib-dexamethasone (VD) with reduced doses of bortezomib, thalidomide, and dexamethasone (vtD) indicated that vtD is more efficacious than VD after ASCT [23]. In conclusion, the actions of thalidomide in blocking stromal cell interactions and inhibiting cytokine secretion, as well as its antiangiogenic activity and immunomodulatory effects, make thalidomide a promising agent in the management of this highly challenging MM.

The focus of clinical trials on thalidomide has not changed. A myeloma IX randomized trial conducted by the Medical Research Council (MRC) [24] compared oral cyclophosphamide, thalidomide, and dexamethasone with infusional cyclophosphamide, vincristine, doxorubicin, and dexamethasone (CVAD). The oral regimen improved response, as well as decreased infection and cytopenia; the survival outcome was almost the same as that achieved with the CVAD regimen. An HOVON-65/GMMG-HD4 trial that included newly diagnosed MM patients showed that the expression of the cereblon (CRBN) gene is associated with long PFS [25].

Conversely, retrospective data suggested that thalidomide maintenance is associated with short survival for certain types of cytogenetic MM [26].

Thalidomide in the treatment of Waldenstroem macroglobulinemia

Waldenstroem macroglobulinemia (WM) is a B-cell disorder characterized primarily by bone marrow infiltration with lymphoplasmacytic cells. The disease is associated with monoclonal IgM in the blood [27] and classified as a low-grade B-cell non-Hodgkin's lymphoma (NHL) [28]. For the first batch of treated patients, alkylating agents (chlorambucil), nucleoside analogs, and rituximab were reasonable choices; combination therapy of either nucleoside analogs with alkylating agents and/or rituximab or rituximab with chemotherapy, such as CHOP or cyclophosphamide, were also first-line treatment options [29]. Researchers have identified five novel therapeutic agents: the proteasome inhibitor bortezomib; monoclonal antibodies; signaling pathway inhibitors, such as PI3K/Akt/mTOR pathway inhibitors; and immunomodulatory agents (IMiDs). According to the annual clinical update of 2012, novel agents used to treat MM also benefit WM patients [30]. Studies revealed that thalidomide can enhance the effect of rituximab; a trial using thalidomide and rituximab in symptomatic WM patients showed a response rate of 72% [31]. Thalidomide in combination with rituximab is an actively working combination that produces long-term responses in WM. Thalidomide induces the expansion of NK, and increases antibody-dependent cytotoxicity (ADCC). The intended therapy consists of a daily dose of thalidomide (200 mg for 2 weeks, then 400 mg for 50 weeks) and rituximab (375 $mg \cdot m^{-2}$ per week) administered on weeks 2 to 5 and 13 to 16; the median time to progression for responders is 38 months [31]. Other studies recommended thalidomide as a potential alternative treatment for patients who develop drug resistance to frontline agents, such as alkylating agents, purine analogs, and antibody therapy [29,32]. Kawano *et al.* reported the first case that presents a POEMS syndrome associated with WM treated with rituximab and thalidomide. After 8 weeks of treatment, the patient's ambulatory activity was restored and polyneuropathy symptoms completely disappeared [33].

Application of thalidomide in lymphoma

Hodgkin's lymphoma

Hodgkin's lymphoma (HL) is believed to be a curable

neoplasm. Since the 1960s, combinations of chemotherapy, doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) with radiotherapy have been used to treat HL, yielding a relatively high curative rate of more than 80% [34]. However, a number of patients did not respond after first-line therapy, which generated suboptimal outcomes. Although the second-line options or ASCT could be accessed, the one-year recurrence rate was as high as approximately 50%. Despite effective treatment, 30% to 40% of patients with advanced HL relapsed [35].

Two multi-resistant HL cases treated with a regimen that combines thalidomide, cyclophosphamide, and dexamethasone (ThaCyDex) exhibited good outcomes [36]. The two patients suffered from highly resistant HL given that they did not respond to a wide range of drugs (>5 different schemes), including high-dose therapy and autologous and allogeneic stem-cell transplantation. Finally, the patients exhibited a complete response, determined according to International Workshop Criteria in 1999, to the ThaCyDex combination. Limited experience with the application of thalidomide in treating HL has been reported, but the overall immunomodulatory effect suggests a potential therapeutic option in the field despite unsatisfactory single-agent activity [37]. Thalidomide should be combined with other agents for it to exert its function. A small-scale study on 11 patients who were administered a combination of thalidomide and vinblastine indicated that overall response is almost equal to that achieved with vinblastine alone [38]. Previous studies revealed that the best combination includes steroids and/or alkylating agents [39].

Mantle-cell lymphoma

Mantle-cell lymphoma (MCL), a B-cell lymphoma identified in 1994 by the Revised European-American Classification of Lymphoid Neoplasms, is a lymphoproliferative disorder derived from a subset of naive pregerminal center cells characterized by a nodular or diffuse proliferation of atypical lymphoid cells with a monoclonal B-cell phenotype and co-expression of CD5 [40]. MCL is among the toughest lymphomas, and is characterized by the t(11;14)(q13;q32) chromosomal translocation and overexpression of cyclin D1. Immunotherapy is an important therapeutic modality in MCL, and the combination of thalidomide with rituximab has shown substantial antitumor activity [41]. Its mechanism in treating MCL is the indirect inhibition of MCL cell viability through the enhancement of peripheral blood mononuclear cell-mediated cytotoxicity, during which rituximab-induced ADCC is increased by thalidomide. Basic research has also posited the function of NK cells in enhancing treatment with thalidomide.

A study on two patients with stage IV MCL revealed that the patients relapsed after standard serial therapy. Both patients took thalidomide over a long period and tolerated its adverse effects. One of them exhibited a partial response, and the other presented a progressive response with thalidomide alone. These optimal outcomes reflect the therapeutic potential of thalidomide in MCL treatment [42]. Another combination that consists of rituximab and thalidomide, plus a regimen of prednisone, etoposide, procarbazine, and cyclophosphamide, resulted in an overall response rate (ORR) of 73% (CR + PR) in recurrent MCL [43].

Other lymphomas

As a type of non-Hodgkin's lymphoma, diffuse large B-cell lymphoma (DLBCL) accounts for 31% of malignant lymphomas. Lenalidomide (an analog of thalidomide) is popular in both combination and single-agent therapies for lymphoma; optimal outcomes are attributed to both regimens in DLBCL [44]. In addition, case reports showed that thalidomide was used as a single agent to induce the remission of DLBCL patients who relapsed after radiotherapy, HDT, and ACST [45]. Another study supported the application of thalidomide combined with steroids in angioimmunoblastic T-cell lymphoma [46].

Myelodysplastic syndromes

Myelodysplastic syndromes (MDS) is a heterogeneous collection of hematopoietic disorders that are considered clonal and characterized by decreased blood cell counts, as well as a tendency toward progression to acute myeloid leukemia (AML) [47]. MDS is one of the most common bone marrow diseases, with a crude incidence of 4 in 100 000 cases per year [48]. MDS has seven morphological subtypes: refractory anemia (RA), RA with ring sideroblasts, refractory cytopenia with multilineage dysplasia (RCMD), refractory cytopenia with multilineage dysplasia and ringed sideroblasts (RCMD-RS), RA with an excess of blasts, unclassified myelodysplastic syndrome, and MDS associated with isolated del (5q). In addition to the aforementioned seven MDS subtypes, chronic myelomonocytic leukemia and juvenile myelomonocytic leukemia are types of blood cancers that the WHO classifies as "mixed myelodysplastic/myeloproliferative diseases." Different types of blood cancers not only have different manifestations, but also exhibit differences in prognosis and mortality [49]. The overall survival for an entire cohort is low, with 70% of patients dying within 3 years [50].

A pilot study on 34 MDS patients was conducted to examine whether thalidomide provides value in the treatment of the disease. Nineteen of the patients responded to the agent, with a median administration time of 10 months (total range, 5 to 17 months) at a median dose of 400 mg (200 mg to 500 mg) [51]. The rate of bone marrow cell apoptosis significantly decreased after treatment with thalidomide, which can probably reduce dependence on transfusion. The hematological improvement (HI) produced by thalidomide was also observed in the erythroid series in MDS [52]. In another

clinical trial, 100 mg/d thalidomide was administered at the onset with a steady increase to 400 mg/d. Although no complete responses were observed in 83 cases, 19% of the patients and 37% of the complete-duration patients exhibited HI [53]. More studies with almost the same design and treatment demonstrated HI, among which Strupp *et al.* reported a response rate of 65%, including major and partial improvements [51].

In a recent phase 2 study in Taiwan, 60 MDS patients were treated with thalidomide (100 mg/d, increased by 100 mg/d weekly to a maximum of 400 mg/d) for 12 weeks. The results indicated that low-dose thalidomide is effective for MDS with low to intermediate-1 International Prognostic Score System scores [54]. However, in a randomized trial of liposomal daunorubicin and cytarabine versus liposomal daunorubicin and topotecan with or without thalidomide, thalidomide shows negligible benefit for patients with AML or MDS [55]. The Clinical Practice Guidelines of 2013 presents a review of retrospective clinical trials, in which patients were categorized as having either del5q or non-del5q MDS. As indicated by the International Working Group (IWG) 2006 criteria, the ORR was 30% in the del5q group; in the non-del5q group, 11 out of 30 patients responded when thalidomide was combined with EPO [56]. No adverse effects were observed, but significant rates of discontinuation due to adverse events were attributed to large dosages. The researchers advised against the use of thalidomide as a route to MDS treatment [57].

Hereditary hemorrhagic telangiectasia

Hereditary hemorrhagic telangiectasia (HHT) is a syndrome characterized by multiorgan telangiectases and arteriovenous malformations. It affects the nose, skin, gastrointestinal tract, lung, liver, and brain [58]. For patients, epistaxis is a highly challenging problem from which many patients die [59].

Thalidomide has been recommended as a treatment for inhibiting bleeding with gastrointestinal diseases and to be used as an antiangiogenic cancer therapy in HHT patients [60,61]. A systematic review of epistaxis suggested thalidomide as a potential option for the treatment of severe HHT-associated epistaxis unresponsive to conventional therapies, although only a small number of cases have been reported (29 patients from 7 cases). With a mean dosage of 100 mg/d (range, 50 mg/d to 200 mg/d), 23 out of 29 patients responded to thalidomide. Treatment was terminated for one case because of adverse effects (DVT) [62].

Lebrin *et al.* [63] investigated the mechanism of thalidomide to broaden its therapeutic utility in vascular malformation diseases. The study indicated that thalidomide reduces nose-bleeding frequency in subjects with HHT, promotes vessel maturation, recruits thalidomide-induced mural cells with the help of PDGF B, directly affects mural cell behavior, rescues vessel wall defects in $Eng^{+/-}$ mice, and stimulates vessel coverage in humans [63]. These claims are regarded as reasonable given that the primary effect of thalidomide is inducing vessel maturation rather than targeting endothelial sprouts. However, high-dose thalidomide may work through a mechanism that is distinct from small-dose application.

Graft-versus-host disease

Graft-versus-host disease (GVHD) is the most severe complication occurring after bone marrow transplantation. The first two cases of GVHD treated with thalidomide were reported in 1988. One was a patient with acute cutaneous GVHD [64], and the other was a patient afflicted with chronic cutaneous GVHD [65]. The former was controlled by thalidomide administered at a dosage of 400 mg/d to 800 mg/d, and the latter was given 100 mg/d to 300 mg/d. The effect of thalidomide on GVHD was confirmed in 1986 via a rat model that focuses on both prophylaxis and treatment [66]. The encouraging outcomes from case reports and animal experiments accelerated phase II clinical trials on chronic GVHD, but the studies presented varying results. Heney *et al.* reported that five out of six patients responded to thalidomide, among which those with chronic cutaneous GVHD showed the best results [67].

A single-institution study on thalidomide in 37 bone marrow transplantations demonstrated that the addition of thalidomide to standard immunosuppressive therapy is effective among high-risk or refractory chronic GVHD patients [68]. Thalidomide produces an even better outcome in children with GVHD. In this clinical study, almost all of the children showed a clinical response to thalidomide, and adverse effects were minimal and well tolerated [69]. However, a phase 3 clinical trial presents different interpretations, with some indicating that the response of patients who received thalidomide is no better than those who received a placebo [70]. A randomized prospective study with thalidomide, cyclosporine, and prednisone versus cyclosporine and prednisone as initial therapy indicated that thalidomide provides no benefit [71]. Except for the 1988 case report, few studies on acute GVHD have been carried out. In a study designed to treat acute ($n = 21$) or chronic ($n = 59$) GVHD, the activity of thalidomide on acute GVHD was negligible, although its positive effect was apparent on chronic GVHD [72].

Adverse effects

Adverse effects, also referred to as toxicity, are always concomitant with pharmacological effects. The most severe adverse effect of thalidomide is teratogenicity, which is known worldwide as a result of suppressing morning sickness. Although thalidomide has been used in other fields and is considered relatively safe, the agent still imposes numerous other adverse effects. Nevertheless, most of these toxicities are manageable and preventable. Maximizing the benefits of treatment using this agent should include minimizing its toxicity.

Teratogenicity

The teratogenicity of thalidomide is not inherited by the next generation. CRBN was identified as the primary target of thalidomide teratogenicity. Thalidomide initiates its teratogenic effects by binding to CRBN and inhibiting its ubiquitin ligase activity. CRBN was also demonstrated to be necessary to the anti-myeloma activity of thalidomide and other related drugs (i.e., IMiDs) [73,74]. Previous studies on animal models proposed that thalidomide affects a certain promoter associated with the development of limb buds, thereby resulting in the truncation of fetal limbs [75]. During the administration of thalidomide, pregnancy is absolutely contradicted and breast feeding is prohibited. Patients with childbearing potential also have to follow strict birth control requirements.

Cardiovascular and thrombotic adverse effects

Thrombosis, sinus bradycardia, and fluctuations in blood pressure are common toxic effects of thalidomide on the cardiovascular system, but syncope rarely occurs [76]. Given that thalidomide is a broad-spectrum angiogenesis inhibitor, patients being treated with it have exhibited life-threatening hemorrhaging and arterial thromboembolism [77]. DVT is the most severe cardiovascular toxicity.

Other symptoms of arterial events include myocardial infarction, unstable angina, and stroke [78]. For patients with sinus bradycardia, when the condition is severe enough to cause syncope, pacemaker installments are necessary to improve quality of life [79]. Thrombosis typically occurs in the veins, and particularly involves the venous circulation of the lower limbs. Cerebral venous thrombosis has also been reported.

The incidence of DVT in myeloma patients is only 1% to 3% with single thalidomide administration [80]. However, a significantly higher incidence of VTE was observed among patients who were given combinations of thalidomide and other chemotherapeutic agents; for instance, with gemcitabine and fluorouracil in patients developing metastatic renal cancer, incidence was 43% [81], and with doxorubicin-containing chemotherapy in myeloma patients, incidence was 34% [82]. DVT is a more life-threatening adverse effect for patients administered with thalidomide [78]. Thalidomide and lenalidomide both lead to thrombosis in malignancies, such as in MM patients, particularly in combination with dexamethasone or chemotherapy. The International Myeloma Working Group recommends aspirin for VTE of $\leqslant$ 1 risk factor, and LMWH for those with 2 or more individual/myeloma-related risk factors [83]. Other studies proposed prophylactic anticoagulation with warfarin to reduce the risk of thrombosis during thalidomide treatment [84].

Observing such adverse effect in the first five months is a common occurrence because it occurs even under low-dose therapy [85]. Proximal DVT (right superficial femoral/popliteal vein) associated with the recurrence of superficial thrombophlebitis (great saphenous vein) can often be diagnosed after venous ultrasonography. Given that such diagnosis is followed by the administration of thalidomide, a possible correlation was suggested [86].

The mechanism behind thalidomide-associated DVT has not yet been revealed. The hypotheses put forward include thalidomide's alteration of the interactions between cancer cells and coagulation factors, its inducement of prothrombotic factors, and its activation of platelets and vascular endothelial cells, which lead to the activation of the thrombotic system.

Peripheral neuropathy

Periphery neuropathy (PN) is a common adverse effect of chemotherapy agents. In certain circumstances, PN can significantly affect quality of life—an indication for dose reduction, delay, or drug withdrawal [87]. PN is also one of the common adverse events of thalidomide (referred to as thalidomide-induced peripheral neuropathy). Statistics indicate that thalidomide affects 20% to 40% of the sensory neurons of patients to a mild to moderate degree [88,89]. The most common clinical presentation is hypoesthesia (numbness), paraesthesia (tingling or pinprick sensation), and hyperesthesia in the toes and fingers [90–92].

The characteristic neurological symptoms caused by thalidomide are distributed according to the location and length of nerves. The terminal nerves are the most severely compromised, and the sensory nerves are the most frequently affected. Thalidomide can induce the distal symmetric loss of all modalities in the lower limbs. Manifestations include reduced reflexes in proportion to sensory loss. By contrast, the damage to motor nerves and automatic nerves is mild [93–95]. Electrodiagnostic studies [96] indicated that age and cumulative dose are two possible contributing factors.

These results may be attributed to the fact that nerves fail to obtain a sufficient blood supply, leading to nervous or axonal damage. This observation is supported by pathological findings that indicate selective loss of large-diameter myelinated fibers and an increase in the number of small-diameter unmyelinated fibers with gradual regeneration [76]. For patients with preexisting neuropathy, the application of thalidomide should be carefully considered.

Hematologic toxicity

Cytopenia is an uncommon adverse effect of thalidomide relative to the aforementioned effects (e.g., DTV). The degree of toxicity is usually mild, although it can be aggravated when thalidomide is used in combination with glucocorticoid [97]. Cytopenia is attributed to immunosuppression because co-infection with disseminated herpes simplex virus and varicella zoster virus, which typically occur in immunosuppressed states, are reported in patients administered with thalidomide [98].

Mild dose-dependent neutropenia induced by thalidomide occurs in 3% to 14% of patients [7], and such neutrophil shortage increases the chances of infection in MM patients. With medical case monitoring, a solid connection between platelet drop and thalidomide dosage is also observed, with platelet count improving after drug discontinuation [99]. Neutropenia accompanies thrombocytopenia in other cases [100].

Toxic epidermal necrolysis

A number of case reports indicated that toxic epidermal necrolysis has been observed in patients following thalidomide and dexamethasone treatment for MM [101].

Renal dysfunction

Unexplained resistant hyperkalemia has been noted after the introduction of thalidomide, suggesting a possible linkage. Thus, thalidomide may be a contributory factor for the disturbance of renal dysfunction, which results in electrolyte disorder [102].

Summary

When thalidomide was withdrawn from the market in the 1960s, no one expected its application to be extensively revived. Subsequently, a growing number of studies focused on this agent, with its novel biological effects serving as bases for modern clinical therapy.

A newly defined mechanism by which thalidomide may interfere with tumor growth is the enhancement of vessel maturation. Embryoid bodies were used as models to examine the antihemorrhagic effect of thalidomide. At high doses (100 μg/ml), thalidomide inhibited vessel formation, but endothelial sprouting improved at low dosages (10 μg/ml to 50 μg/ml) [63].

Combinations of agents for MM treatment have become the mainstream approach. The addition of thalidomide to previously applied regimens, such as MP-T, dexamethasone, or VD, prove more effective than traditional combinations. Thalidomide plays an even more significant role in refractory or resistant MM because its toxicity is considerably lower than that of conventional chemotherapeutic agents.

For the treatment of WM, thalidomide plus rituximab are considered the best pairing and the best alternative when drug resistance toward first-line therapy develops. Different types of lymphoma, including HL, DLBCL, MCL, and even T-cell lymphoma, are also sensitive to thalidomide. However, a clearer view requires additional clinical trials on whether thalidomide is valuable in the treatment of lymphoma.

MDS, another malignant hematological disease, is among the most difficult to treat. Few agents have been proved effective and well tolerated. The presence of thalidomide is encouraging for patients with low to intermediate-1 risk, although the 2013 Guidelines do not recommend it as a therapeutic choice. Combination regimens should be explored and examined because the current application of thalidomide in MDS is of single low-dose type, which is relatively mild for such malignancy.

As an agent that affects angiogenesis, thalidomide can be applied to HHT, particularly one of its complications, epistaxis. As for GVHD, thalidomide affects the chronic type, particularly cutaneous-related GVHD. In acute GVHD, patients treated with thalidomide exhibit the usual response.

In conclusion, in terms of adverse effects, thalidomide effectively functions in the autoimmune, anti-inflammatory, and anticancer fields, as indicated by current data. Rational drug combinations are significant to the application of thalidomide. Detailed trials in the aforementioned areas will help reveal the potential of this “outdated” agent.

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Compliance with ethics guidelines

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