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Review Article

Thalidomide: a new old drug in the treatment of multiple myeloma

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Abstract

Thalidomide, a drug used initially as a sedative, was removed from widespread use since the early 1960s because of its teratogenic effect. It has now returned to clinical practice as an effective agent in the treatment of erythema nodosum leprosum. Activity has also been demonstrated in the treatment of inflammatory bowel disease and chronic graft-*versus*-host disease. More recently, the drug was found to have significant antiangiogenic and immunomodulatory effects. Clinical trials have demonstrated significant clinical response in the treatment of patients with relapsed or refractory multiple myeloma (MM). In combination with dexamethasone, thalidomide was found to be as effective as aggressive intravenous chemotherapy regimens used in the initial therapy for patients with newly diagnosed MM. Except for a high rate of venous thromboembolism, thalidomide's other toxicity is well tolerated. In this review, we will detail recently published clinical trials evaluating the use of thalidomide alone or in combination with dexamethasone to treat relapsed, refractory or newly diagnosed patients with MM.

Introduction

Multiple myeloma (MM) is a multifactorial disorder with serious clinical manifestations (Tables I and II). Several agents including thalidomide have been tested in the treatment of MM.

Thalidomide was first synthesized in 1954 by W.H. Kunz, a German chemist. The antihistaminic properties for which it was initially synthesized were weak, but it produced significant sedation in animals, leading to its clinical use as a sedative. Its use was widespread until the observations of increased limb malformation were reported, which led to its withdrawal in the early 1960s (1).

Thalidomide was found to have an immunomodulatory effect; in addition, it can inhibit angiogenesis and induce apoptosis of established neovasculture in experimental models (2, 3). Evidence suggests that angiogenesis is increased in MM and has prognostic value in this disease (4-6). On this basis, thalidomide has been studied as antiangiogenic therapy for MM.

MM is a relatively uncommon malignancy, representing 1-2% of all malignancies and accounting for 10% of all malignant hematologic neoplasms (7-9) (Tables I and II). Although MM is sensitive to both chemotherapy and radiotherapy, complete response with standard therapy is rare (10, 11). The current standard of care for patients with MM is combination chemotherapy using nonalkylating agents such as vincristine, doxorubicin and dexamethasone (VAD) for 4-6 months, followed by high-dose chemotherapy and autologous stem cell transplantation. Although the VAD regimen is associated with a response rate that exceeds 50% (12), it is associated with significant toxicity and is cumbersome, requiring an indwelling central venous access for the continuous infusion of chemotherapy that places the patient at risk for catheter-related infection, sepsis and thrombosis.

Table I: Multiple myeloma.

Definition: malignant proliferation of plasma cells derived from a single clone
Etiology: radiation, mutations in oncogenes, familial causes, role of interleukin-6
Incidence/prevalence: 14,400 cases in 1996
Incidence increases with age
Males > females; blacks > whites

Table II: Clinical manifestation of multiple myeloma.

Common
Bone pain and pathological fractures
Anemia and bone marrow failure
Infection due to immune paresis and neutropenia
Renal impairment
Renal failure: 25%
Multiple contributory factors
Hypercalcemia, hyperuricemia, recurrent infections
Tubular damage produced by light chains
Nonselective proteinuria
Anemia: 80%
Normochromic/normocytic
Myelophthisis; inhibition by cytokines produced by plasma cells
Leukopenia/thrombocytopenia only in advanced cases
Less common
Acute hypercalcemia
Symptomatic hyperviscosity
Neuropathy
Amyloidosis
Coagulopathy

Mechanism of action

The mechanism of action of thalidomide in MM is unclear. Laboratory studies have shown that thalidomide has potent antiangiogenic properties, which might explain the teratogenic effect that leads to the defect in limb bud formation (1). Animal studies have shown that it can decrease vascular density in granulation tissue (13). In addition to this antiangiogenic effect, thalidomide exhibits other immunomodulatory effects: it inhibits the production of tumor necrosis factor-α (14), it stimulates cytotoxic T-cell proliferation and it induces the secretion of interferon gamma and interleukin-2 (15). It also modulates the expression of several cell surface adhesion molecules (16), such as E-selectin and vascular cell adhesion molecule (VCAM) (17).

Clinical studies of thalidomide in multiple myeloma

Refractory or relapsed disease

Given the established immunomodulatory effect of thalidomide, it was natural that it first be tried on patients with relapsed or refractory disease. In one of the first clinical studies using thalidomide, 84 previously treated patients with refractory MM (90% of them relapsed after high-dose chemotherapy) received oral thalidomide as a single agent for a median of 80 days. Thalidomide was started at a dose of 200 mg/day. The serum or urine levels of paraproteins were reduced by at least 50% in 21 patients (25%). Reduction of paraprotein levels was observed within 2 months in 78% of responding patients (18).

Several other investigators subsequently confirmed these observations. Alexanian *et al*. (19) recently updated their experience with thalidomide, first alone and then in combination with dexamethasone among patients with relapsed or refractory MM. They reported a clinical response rate of 26% in a group of 43 such patients. Among 24 patients unresponsive to thalidomide, the addition of intermittent high-dose dexamethasone resulted in 10 additional responses (42%). Clinical response was defined as > 50% reduction of serum myeloma proteins and/or > 75% reduction of Bence-Jones proteins. The median time to response was 4 months and median duration of remission was approximately 1 year (19). Other groups reported even higher response rates, ranging from 36-43% (20, 21).

Recently, Kumar *et al*. (22) used thalidomide (200 mg escalated as tolerated to 800 mg/day) to treat 32 patients with relapsed MM. A total of 17 patients (53%) had > 25% reduction in M-protein, 10 patients (31%) had stable disease and 4 patients (13%) progressed. The median progression-free survival was 15.7 months among the responders. The median overall survival for the entire group was 22 months (22).

Based on the response rates observed with thalidomide alone, as well as the established role for dexamethasone in the treatment of MM, Weber *et al*. (23) and Anagnostopoulos *et al*. (24) enrolled 47 consecutive patients (median age, 48 years) in a trial testing the efficacy of the combination of dexamethasone and thalidomide in patients with refractory MM, 77% of whom had shown resistance to at least two prior regimens, including 11% who had received intensive therapy and autologous stem cell transplantation. Thalidomide was given at a starting dose of 200 mg at bedtime and was increased by 100 mg weekly to a maximum of 600 mg, whereas dexamethasone was given concurrently at a dose of 20 mg/m^2 on days 1-5 and then repeated every 2 weeks. Defining clinical response as > 75% reduction in serum paraproteins and/or > 90% reduction in Bence-Jones proteins, response was observed in 22 patients (47%), 6 of whom (27%) achieved complete remission. The median time to response was only 2 months.

In another study, 120 patients with relapsed or refractory MM were treated with thalidomide 100 mg/day and dexamethasone 40 mg (days 1-4 of each month). Their clinical outcome was compared to a control group of 120 selected patients with relapsed or refractory disease treated with conventional chemotherapy, matched for serum microglobulin levels and Dune and Salmon clinical stage. Myeloma protein reduction of approx. 50% was observed in 52% of the thalidomide plus dexamethasone group and in 45% of the conventional chemotherapy

Table III: Recent studies of thalidomide in relapsed or refractory multiple myeloma.

Reference	No. of patients	Regimen	Paraprotein Reduction		
			≥ 75%	≥ 50%	≥ 25%
18	84	Thalidomide alone	17%	25%	32%
19	43	Thalidomide alone	NR	26%	NR
	24*	Thalidomide + dexamethasone	NR	40%	NR
22	32	Thalidomide alone	NR	31%	53%
23, 24	47	Thalidomide + dexamethasone	47%	NR	NR
25	120	Thalidomide + dexamethasone	NR	52%	NR

NR = not reported. *Unresponsive to thalidomide alone.

group. After a median follow-up of 18 months for the thalidomide plus dexamethasone survivors, 38% were alive in remission compared to 13% in the conventional chemotherapy group followed for a median of 22 months. Median overall survival was 27 months from the start of thalidomide plus dexamethasone and 19 months from the start of conventional chemotherapy ($p < 0.05$) (25). The results of these studies are summarized in Table III.

Newly diagnosed patients

Based on the activity of thalidomide alone or in combination with dexamethasone that was demonstrated in relapsed or refractory MM, investigators evaluated the role of this agent in the initial therapy of this disease. Two key phase II studies of thalidomide plus dexamethasone in previously untreated symptomatic MM patients have been recently published. In the first study, researchers at the Mayo Clinic used the combination of thalidomide and dexamethasone in a phase II trial to determine if this combination would provide a more convenient, less toxic alternative for pretransplantation induction therapy with VAD (26). Fifty previously untreated symptomatic patients (median age, 61 years) were enrolled. Most were high risk (with high B_2-microglobulin and high plasma labeling index). The treatment consisted of thalidomide at 200 mg/day and dexamethasone at 40 mg/day (days 1-4, 9-12 and 17-20) during odd cycles and days 1-4 during even cycles. Thalidomide dose was escalated by 200 mg/day every 2 weeks to a maximum of 800 mg/day. This dose escalation was stopped following grade 3 or 4 skin toxicity. Defining major response as ≥ 50% reduction in serum and urine proteins and minor response as ≥ 25% reduction, major response was noted in 32 patients (64%); additionally, 28% achieved minor response. These results indicate that the overall response to thalidomide and dexamethasone is as good as, or even better than, the historical results obtained using other combination chemotherapy regimens.

In the second study, Weber *et al*. (27) at M.D. Anderson Cancer Center reported similar results. In their study, 40 patients with previously untreated, symptomatic disease received thalidomide at 100 mg/day, which was escalated by 100 mg/day at weekly intervals to a maximum dose of 400 mg/day. Dexamethasone was started on days 1-4, 9-12 and 17-20. Using strict response criteria (complete response: complete disappearance of M-proteins, as well as plasma cells in bone marrow < 5%; partial response: ≥ 75% reduction in M-proteins). Using these definitions, 73% achieved partial response and 13% had complete response (27).

More recently, thalidomide was also used with melphalan and prednisone (MP) as a first-line therapy for patients with newly diagnosed symptomatic MM. In one study, 56 patients were assigned to a treatment with 6 monthly courses of MP (melphalan 4 mg/m^2 and prednisone 40 mg/m^2 for 7 days every month) plus thalidomide that was administered at 100 mg/day continuously until any signs of disease progression or relapse. The dose of thalidomide was reduced to 50% when grade 2 WHO toxicity occurred, and it was suspended for any grade 3 toxicity. Data on 31 patients (median age, 72 years) who had completed the six assigned MP courses were presented during the 45th annual meeting of the American Society of Hematology. After a minimum of 6 months of treatment, complete remission was observed in 7 patients (22%), M-protein reduction of 75-99% was detected in 13 patients (42%) and a response rate of 50-74% was seen in 8 patients (26%). Response was followed by significant improvement of performance status, skeletal pain, anemia and transfusion requirement (28). The results of these studies are summarized in Table IV.

Toxicity

When used alone, thalidomide toxicity, although frequent, was dose-dependent, nearly always mild, short-term and reversible. Constipation, weakness or fatigue and somnolence occurred in one-third or more of the patients. However, grade 3 or 4 adverse effects were infrequent (18-22).

However, when thalidomide was given in combination with dexamethasone, side effects were very frequent. Constipation, neuropathy, fatigue and sedation occurred in > 50% of the patients (23-27). One particular side effect was a higher incidence of venous thromboembolism (VTE). In the Mayo clinic study cited above (26), 1 patient died with a clinical diagnosis of pulmonary embolism (PE) and 6 patients (12%) had venous thrombosis. The incidence of VTE was similar (15%), with 1 death due to

Table IV: Recent studies of thalidomide in newly diagnosed multiple myeloma.

Reference	No. of patients	Regimen	Paraprotein Reduction		
			≥ 75%	≥ 50%	≥ 25%
26	50	Thalidomide + dexamethasone	52%	68%	92%
27	28	Thalidomide alone	36%	NR	NR
	40	Thalidomide + dexamethasone	72%	NR	NR
28	56	Melphalan + prednisone + thalidomide	65%	90%	NR

NR = not reported.

PE in the M.D. Anderson Cancer Center study (27). To prevent VTE, warfarin was given to the first 24 patients at a fixed prophylactic dose of 1 mg. Despite this, VTE occurred in 25% of the patients. Full-dose anticoagulation with warfarin or low-molecular-weight heparin fully prevented VTE in the next 16 patients.

The incidence of deep vein thrombosis with single-agent thalidomide was < 5% (29). It is also important to note that the incidence of VTE is relatively high in patients with MM on therapy other than dexamethasone and thalidomide (30, 31).

Thalidomide and bone marrow transplantation

Because high-dose and autologous stem cell transplantation is a standard option for the treatment of MM, extra care should be exercised during the initial induction of chemotherapy, some of which may adversely affect stem cell collections. In the Mayo clinic study (26), 52% of the patients underwent successful stem cell collection after four cycles of thalidomide and dexamethasone, indicating that initial treatment of MM with thalidomide will not interfere with high-dose chemotherapy and autologous transplantation.

Future directions

Based on the impressive results discussed above, researchers have developed structural analogues to thalidomide that are probably more effective and associated with fewer adverse effects than thalidomide. One of these new analogues is lenalidomide (CC-5013; Revimid®). Responses have been reported in one-third of the patients with advanced and refractory myeloma (32, 33), many of whom had been previously exposed to thalidomide. Unlike thalidomide, Revimid® exhibits virtually no sedative effects and occasionally it has neurotoxic effects. However, this new drug can cause myelosuppression, which, in the setting of compromised bone marrow from prior chemotherapy therapy, might be severe (32). In a phase III study for advanced MM comparing two different schedules of Revimid®, a prolonged schedule of 25 mg for 20 doses was associated with higher response rates compared with an abbreviated course of 50 mg for 10 doses (34).

A randomized study (SWOG S0232) comparing Revimid® alone *versus* its combination with dexamethasone is ongoing. The combination of dexamethasone and thalidomide is also being evaluated in induction and maintenance in the context of standard tandem autotransplant with high-dose melphalan. Thalidomide was also combined with a new proteosome inhibitor, bortezomib (Velcade®), for post-tandem transplant relapsed and refractory disease (35).

Conclusions

Despite its history as a human teratogen, thalidomide is emerging as a treatment for cancer and inflammatory diseases. Although the evolution of its clinical application could not have been predicted from the tragedy associated with its misuse in the past, its history serves as a lesson in drug development that underscores the need to understand the molecular pharmacology of a compound's activity, including associated toxicities. Thalidomide has shown great promise in advanced or refractory multiple myeloma either alone or in combination with other agents. It has also demonstrated benefits in a wide variety of disparate conditions such as aphthous and genital ulcers, cancer cachexia, HIV, tuberculosis and chronic graft-*versus*-host disease. Thalidomide is also being investigated for the treatment of renal cell carcinoma, as well as liver and thyroid cancers. Better understanding of its many mechanisms of action has provoked great interest in its potential use for the treatment of various disorders.

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