NOVEL USES OF THALIDOMIDE: FOCUS ON ITS APPLICATIONS IN MALIGNANCY

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Thalidomide removed from market in 1962 because of severe teratogenicity. Recent studies have shown that it has antiangiogenic and immunomodulatory effects. It has now returned to practice as an effective oral agent in the management of various conditions like erythema nodosum leprosum and multiple myeloma. Its use in other tumors is under evaluation, with promise in renal cell carcinoma, ovarian cancer, non small cell lung carcinoma, colorectal carcinoma, prostate cancer, glioma, and Kaposi's sarcoma. It has also shown beneficial activity in cancer related cachexia. The most notorious effect of thalidomide is teratogenicity. Sedation and constipation are known side-effects of thalidomide. Thalidomide also has been associated with neuropathy and deep vein thrombosis. To ensure that fetal exposure to this teratogenic agent does not occur, the manufacturer has instituted a comprehensive program to control prescribing, dispensing, and use of the drug. This program, known as the System for Thalidomide Education and Prescribing Safety (STEPS). The present review examines the background, pharmacokinetics, mechanism of action, adverse effects, and uses of thalidomide in malignancy. Relevant articles were identified through PUBMED searches (1962- 2009). Search terms included thalidomide, pharmacokinetics, pharmacology, therapeutic use, and teratogenicity, as well as terms for specific disease states and adverse events. Further publications were identified from the reference lists of the reviewed articles.

Key words: Thalidomide, malignancy, teratogenicity, multiple myeloma.

INTRODUCTION

Thalidomide (α-N{phthalimido} glutarimide [$C_{13}H_{10}N_2O_4$]) is a synthetic glutamic acid derivative that was initially used as an over-the-counter sedative-hypnotic. It was used for pregnancy-associated morning sickness but caused teratogenicity and neuropathies and was withdrawn from the market.[1]. However, thalidomide was noted to have anti-inflammatory and

immunomodulatory effects and was reintroduced to clinical practice by the Food and Drug Administration in 1998 for the treatment of erythema nodosum leprosum. To prevent further episodes of teratogenicity, the manufacturing company set up a program known as the System for Thalidomide Education and Prescribing Safety (STEPS).[2]

It is used for the treatment of moderate to severe type 2 lepra reactions. It is also used in several other conditions whose etiology may involve the immune system, such as treatment and prevention of graft versus host disease, treatment and prevention of recurrent apthous stomatitis in severely and terminally immunocompromised patients, treatment of the clinical manifestations of both tuberculosis and non-tuberculosis mycobacterial infections, treatment of HIV associated wasting syndrome, Kaposi's sarcoma , Behçet's disease, Crohn's disease, discoid lupus, complex pain syndrome, and rheumatoid arthritis. Another potential use for thalidomide is in the treatment of diabetic retinopathy and macular degeneration because of its ability to block angiogenesis. Thalidomide has demonstrated measurable activity in both hematologic cancers and solid tumor malignancies. It was also shown benefits in cancer related cachexia in patients with pancreatic cancer.[3] This review focuses on thalidomide's mechanisms of action, biochemistry, pharmacokinetics and its use in multiple myeloma and other malignancies. Relevant articles were identified through PUBMED searches (1962-2009). Search terms included thalidomide, pharmacokinetics, pharmacology, therapeutic use, adverse effects, teratogenicity, malignancy as well as terms for specific disease states. Further publications were identified from the reference lists of the reviewed articles.

Pharmacokinetics: Thalidomide is a derivative of glutamic acid that exists as an equal mixture of enantiomers which rapidly interconvert at physiological pH.[3,4] It is slowly absorbed from the gastrointestinal tract. Thalidomide is poorly soluble in water and thus no parenteral preparation is available. Peak plasma concentrations are reached within 3 to 6 hours of an oral dose. It crosses the placenta and is distributed into the semen. The elimination half-life is about 5 to 7 hours. Thalidomide follows first order kinetics. Volume of distribution is about 122 liters. Total body clearance is about 10L/h. Although clearance is predominantly non-renal (less than 1% found in the urine), thalidomide is usually detectable in the urine. Thalidomide is metabolized in the liver to EM-12 and supidimide, the teratogenic and non-teratogenic analogs, respectively. There is strong evidence that thalidomide requires cytochrome P450(CYP)-catalyzed biotransformation to exert its pharmacological activity and that the CYP2C subfamily may be primarily involved.[5] Thalidomide does not induce directly the enzyme complex; however, it may interfere with other medications that induce cytochrome P450.Thalidomide can be measured by liquid chromatography.[3,6]

Mechanism of action: The mechanism of action of thalidomide is not completely understood. It has anti-inflammatory and immunomodulating effects, including the inhibition of synthesis of tumour necrosis factor α (TNF

α), inhibition of leucocytes chemotaxis into the site of inflammation, and reduction of phagocytosis by polymorphonulear leucocytes. It also modulates interleukins and inhibits angiogenesis. Serum T-helper cells and IgM concentrations also decreased in response to thalidomide. Thalidomide is reported to suppress levels of several cytokines, angiogenic and growth factors including TNF-alpha, basic fibroblast growth factor (bFGF), vascular endothelial growth factor (VEGF) and interleukin-6 (IL-6). The resulting anti-angiogenic, immunomodulatory and growth suppressive effects form the rationale for investigating thalidomide in the treatment of malignancies.[3,8,9,10]

Adverse effects and precautions: The most notorious adverse effect is teratogenicity when given in early pregnancy. Single dose itself can cause teratogenicity and involved malformations of limbs (phocomelia) and defects of the ear, eyes and internal organs. Hence thalidomide should not be used in women of child bearing potential. If such use is absolutely essential then stringent contraceptive measures must be used, including the simultaneous use of 2 reliable forms of contraception for at least 4 weeks before, during and 4 weeks after thalidomide therapy. Regular pregnancy testing is mandatory. If pregnancy occurs during thalidomide therapy, the drug should be stopped immediately and the patient should be evaluated and counseled appropriately. Male patients receiving thalidomide also should use barrier methods if their partner is of child bearing potential as thalidomide is found in semen. Also patient should not donate blood or semen when they are on thalidomide.[3]

Thalidomide has been associated with neuropathy characterized as distal lower extremity painful paraesthesia, numbness, pain in the extremities, burning sensation and/or delayed motor weakness, which can be severe and irreversible.[10,11] Other common adverse effects include constipation, nausea, increased appetite, xerostomia, hypersensitivity reactions and orthostatic hypotension, nervousness, tremor, confusion, fatigue, depression, dizziness, somnolence, headache, sedation, fluctuation of blood pressure, bradycardia. Endocrine abnormalities reported include hypothyroidism, hypoglycemia, amenorrhoea and increasing ACTH and prolactin levels. Neutropenia and thrombocytopenia are also a reported side effect.[12] It can cause erythematous macular rash which may develop 2 to 10 days after initiating therapy. There were case reports of Stevens- Johnson syndrome and toxic epidermal necrolysis also.[3] Increased risk of deep vein thrombosis was also reported in many studies.[13] There are also case reports of interstitial pneumonitis, dementia, sexual dysfunction and migraine attacks in patients receiving thalidomide.[3]

Thalidomide may enhance the sedative effects of barbiturates, alcohol, chlorpromazine etc. There may be an increased risk of deep vein thrombosis when thalidomide used along with doxorubicin.[3]

Role of thalidomide in malignancy: To grow and metastasize, solid tumours must develop their own blood supply by neo-angiogenesis. Thalidomide inhibits the processing of mRNA encoding peptide molecules including

tumour necrosis factor-alpha (TNF-alpha) and the angiogenic factor vascular endothelial growth factor (VEGF). Initial studies have shown that responses with thalidomide were disappointing in patients with melanoma, ovarian cancer, and breast cancer. Results for patients with renal-cell carcinoma were more encouraging.

Accumulating data suggest the requirement of angiogenesis also for the development and progression of hematopoietic malignancies including acute myeloid leukemia. Inhibition of increased microvessel density in bone marrow might be a promising target for pharmacological interventions aimed at reducing disease activity. Thalidomide being an antiangiogenic agent has demonstrated a considerable efficacy in myelodysplastic syndromes and acute myeloid leukemia. Responders experienced hematologic improvements with increased hemoglobin and platelet counts resulting in temporary transfusion independence. Thalidomide as a single agent has significant anti-leukemic activity with some evidence for anti-angiogenic effects in bone marrow.[14]

Thalidomide in malignant melanoma: Melanoma is a hypervascular tumor and angiogenesis plays a critical role in the development/progression of metastases. As various pathways are involved in tumor angiogenesis, a combination of agents with different antiangiogenesis activities is a reasonable approach. Thalidomide combined with interferon is a safe and tolerable palliative treatment for previously treated stage IV melanoma. Thalidomide has some activity in melanoma patients with brain metastases.[15,16,17]

Thalidomide in myelofibrosis with myeloid metaplasia: Myelofibrosis with myeloid metaplasia (MMM) is a myeloproliferative disorder associated with bone marrow fibrosis, ectopic hematopoiesis and increased microvascular density. Several studies confirmed that thalidomide treatment in MMM resulted in clinical benefit with improvement of thrombocytopenia and of anemia, and significant regression of splenomegaly. But tolerability seems to be the major limitation in this disease. Thalidomide also appears to be ineffective in myelofibrosis arising in the course of polycythemia vera or in patients with MMM causing massive splenomegaly.[18-23]

Thalidomide in multiple myeloma:[24-35] Multiple myeloma accounts for 10% of all haematologic malignancies worldwide. Unlike other malignancies, in which surgery and radiation are important treatment modalities, myeloma is exclusively treated with stem cell transplantation and drug therapy. The melphalan-prednisolone and vincristine-doxorubicin-dexamethasone (VAD) regimens, which have been standard treatments for multiple myeloma over the past few decades, have yielded responses without real survival benefits. Although stem cell transplantation is often performed in multiple myeloma to improve survival and remission rates, some patients are unable to undergo transplant for a variety of reasons, including age (older than 65 years), comorbidities, and/or organ dysfunction.

Multiple studies with large numbers of patients have confirmed that this drug has significant activity in multiple myeloma. It is given in an initial dose of 200mg once daily and according to patient tolerance, the dose is increased by 100mg at weekly intervals up to a maximum dose of 800mg daily. It has also shown encouraging results in newly diagnosed disease, either alone or with dexamethasone. The combination of thalidomide plus melphalan and prednisone is superior to the classical melphalan-prednisone regimen in elderly patients, and will become the standard of care.

Studies have shown superiority of thalidomide plus dexamethasone regimen over the classical VAD regimen (Vincristine, Adriamycin, and high doe dexamethasone) in patients below 65 years of age with symptomatic advanced stage multiple myeloma. Thalidomide also showed encouraging results in elderly patients with advanced stage multiple myeloma. Post-transplantation thalidomide maintenance increases the complete remission rate and prolongs progression-free survival and overall survival. Thalidomide is currently considered as one of the most active agents in relapsed myeloma. In relapsed and refractory myeloma, thalidomide is used mostly in combination with dexamethasone and/or chemotherapy (initial dose 100–200 mg/day). It may results in an increased risk of deep vein thrombosis; therefore, at least in patients with increased risk for deep vein thrombosis anticoagulation prophylaxis should be administered.

Thalidomide with dexamethasone and thalidomide with VAD regimens, as induction therapies before stem cell transplantation and in patients not proceeding to transplantation might obviate the need for stem cell transplantation in a sizeable proportion of patients.

Thalidomide in renal cell carcinoma: The highly vascular nature of renal carcinoma cells suggests that inhibition of angiogenesis may be beneficial in this disease. Thalidomide has been described as inhibitor of the fibroblast growth factor (FGF) and the vascular endothelial growth factor (VEGF). A case study of a patient with metastatic renal-cell carcinoma in the lung and lymph nodes in the low-dose thalidomide study illustrates that (1) responses may be very slow; (2) the palliative response is separate from the overall response, occurs much earlier, and is not consistent with an antiangiogenic action; and (3) peripheral neuropathy is a manageable side effect. Besides peripheral neuropathy, patients can experience severe constipation even on low doses as well as headache, edema, and skin rash for which treatment recommendations can be made. Anecdotal benefits of thalidomide include enhanced or maintained appetite, improved sleeping, and reduced sweating.[36]

Thalidomide has been widely evaluated in advanced metastatic renal cell carcinoma (RCC).Studies have shown that thalidomide alone has modest activity in RCC and the response rates and progression-free survival were comparable to those observed with IFN-α and IL-2. Studies have reported that low dose thalidomide in renal cell cancer look to be as good as the high dose thalidomide.[37-45]

Combination regimen containing thalidomide (low-dose thalidomide and IFN-α; thalidomide and IL-2; 5-fluorouracil, IFN-α and IL-2, and thalidomide) also showed high stable disease response in renal cell carcinoma. High dose thalidomide had particularly high rates of deep vein thrombosis and peripheral neuropathy. Hence high-dose thalidomide cannot be recommended since the level of toxicity is high.[46,47]

Thalidomide in prostate cancer: Microvessel density (MVD) has been reported to be higher in prostate cancer tissue than in adjacent hyperplastic or benign tissue.[48] Preclinical evidence also suggests that angiogenesis may play a key role in the development of aggressive prostate cancer lesions.[49] Clinical studies have observed a correlation between increased angiogenesis in primary tumor specimens and the future development of metastatic disease. The apparent importance of angiogenesis in the evolution of prostate cancer provides a rationale for the investigation of antiangiogenesis agents in AIPC. Early clinical trials showed that low dose thalidomide appears to be relatively well tolerated and it shows activity in hormone refractory prostate cancer with reduction in prostate specific antigen. High dose thalidomide did not give increased benefit.[50] Thalidomide may have use in the treatment of men who have biochemical recurrence of prostate cancer or a rise in their prostate-specific antigen (PSA) count after definitive therapy, according to a new randomized study from the National Cancer Institute. In this population, the use of thalidomide was associated with an increase in PSA progression-free survival after intermittent androgen-deprivation therapy.[51]

Drake MJ et al[52] reported that thalidomide may be an option for patients with androgen-independent prostate cancer who have failed other forms of therapy, provided close follow-up is maintained for development of peripheral neuropathy .Their findings was based on an open-label study using thalidomide 100 mg once daily for up to 6 months in 20 men with androgen-independent prostate cancer.[52]

There was increased response rate when thalidomide was added to docetaxel. Leonard G et al[53] studied the effects of combination of docetaxel and thalidomide in androgen independent, nonmetastatic prostate cancer. Thalidomide was administered in doses ranging between 200 mg and 1200 mg. This therapy resulted in a > 40% fall in PSA levels in 27% of patients and improvement in clinical symptoms in all responding patients. PSA declines often resulted in striking reductions in measurable disease on positron emission tomographic scan. Combined docetaxel and thalidomide compared with docetaxel alone in pretreated AIPC patients revealed significant benefits.[53]

Thalidomide in ovarian carcer: Downs et al[54] studied the effects of thalidomide with topotecan compared with topotecan alone in women with recurrent epithelial ovarian carcinoma and concluded that the addition of thalidomide to topotecan for the treatment of recurrent ovarian cancer improve response rates. Their analysis included 69 women (39 women in the control arm and 30 women in the thalidomide arm). The median overall

survival was 15 months in the control arm and 19 months in the thalidomide arm. Kanwar VS et al[55] reported a case of advanced small cell carcinoma of the ovary in a seventeen-year-old female, successfully treated with surgery and multiagent chemotherapy containing thalidomide. Cham Jk et al[56] demonstrated the safety, tolerability, and potential efficacy of Thalidomide in recurrent and refractory epithelial ovarian cancers in a phase I clinical trial. Gordinier M[57] also reported that the thalidomide is comparable in response and quality of life to single agent intravenous chemotherapy in heavily pretreated patients with ovarian cancer.

Thalidomide in glioma and glioblastoma: Glioma and glioblastoma are highly vascularized tumors that overexpress angiogenic factors. As thalidomide has antiangiogenic property, it may provide clinical benefits in these patients. Initial studies have shown that benefits with thalidomide alone in glioma and glioblastoma were not substantial. But combination regimen containing thalidomide with carboplatin/carmustine has shown some promising results.[58-60]

Thalidomide in colorectal carcinoma: Liu WM et al[61] showed that thalidomide significantly inhibit the metastatic capability of murine colorectal carcinoma cells lines both in vivo and in vitro. In addition, an in vivo experimental metastasis model also showed that treatment with the drugs resulted in a significantly lower number of metastatic pulmonary nodules relative to control mice and the mechanism may involve alterations to cell signalling functionality. Thalidomide caused a significant reduction in the volume of colorectal liver metastases during the late phase of tumor growth murine model of colorectal liver metastases in a study by Daruwalla J et al.[62] The combination of capecitabine and thalidomide in previously treated, refractory metastatic colorectal cancer has shown promising results.[63] Single-agent thalidomide was inactive in heavily pretreated metastatic colorectal cancer.[64]

Thalidomide in Kaposi's sarcoma: Kaposi's sarcoma is a lymphangioproliferative tumour. Sevral studies reported the utility of thalidomide in the treatment of non-AIDS-related as well as AIDS related Kapsoi's Sarcoma.[65-67]

Thalidomide in breast cancer: The anti-tumor properties of thalidomide or in combination with an oncolytic herpes virus (OncdSyn) was investigated in a mouse model of human breast cancer. Thalidomide alone delayed tumor growth in this mode.[68] Single-agent thalidomide did not show activity in patients with heavily pretreated breast cancer.[69]

Thalidomide in lung cancer: Cisplatin and vinorelbine regimen combined with thalidomide significantly prolongs the median time to tumor progression in patients with advanced non small cell lung carcinoma (NSCLC).[70] Thalidomide, irinotecan and gemcitabine combination is reported to be active in advanced NSCLC with manageable toxicity profile.[71,72] Thalidomide in combination with chemotherapy did not improve

survival of patients with small cell lung carcinoma (SLLC) but was associated with an increased risk of thrombotic events in a randomized, double-blind, placebo-controlled trial.[73]

Thalidomide in cancer cachexia: Proinflammatory cytokines, especially tumour necrosis factor α(TNF-α), play a prominent role in the pathogenesis of cancer cachexia. Thalidomide, which is an inhibitor of TNF-α synthesis, may represent a novel and rational approach to the treatment of cancer cachexia. Thalidomide was well tolerated and effective at attenuating loss of weight and lean body mass in patients with cachexia due to advanced pancreatic cancer.[74-76]

CONCLUSION

Thalidomide has shown promising activity in several hematological as well as well as solid malignancies, but the benefit is confirmed only in few malignancies like multiple myeloma. Several studies in solid tumors have indicated activity in Kaposi's sarcoma, ovarian cancer, renal cell carcinoma, non small cell lung carcinoma and prostate cancer. Further trials are needed to define the role of thalidomide in these malignancies, especially in combination with other regimen. Though various mechanisms like antiangiogenic and immunomodulatory action explained, complete knowledge regarding the molecular targets for thalidomide in cancer is still to be evaluated. Thalidomide is associated with serious toxicities like deep vein thrombosis, peripheral neuropathy. Presently research is focusing on the development of new analogs of thalidomide like lenalidomide with improved efficacy and reduced toxicity.

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