A Review: Uses of Thalidomide in Cancer Treatment

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Abstract
Thalidomide is an anti-angiogenetic agent, which was widely used in early 1950s and 1960s for the treatment of morning sickness in pregnant women. The drug has been banned in 1960 as it caused severe birth defects in children whose mothers had used thalidomide during pregnancy. Though it caused severe adverse effects the drug has found to be effective in the treatment of leprosy and multiple myeloma. These days thalidomide has been successfully used in cancer patents and patients with leprosy.

Keyswors: Thalidomide, Cancer, Types of cancer, Stem cell transplantation

INTRODUCTION
Thalidomide was first introduced into the market in the year 1957 as a non-barbiturate non-addictive sedative. It was first developed by a German company named Chemei Grunenthal and was marketed in the brand name ‘contergan’. Clinical trials conducted by this company in early 1956 have been led to the promotion of this drug in treating respiratory infections. Studies done by the researches at Grunenthal have discovered that Thalidomide can effectively relieve morning sickness in pregnant women. Around the world Thalidomide was marketed and distributed in almost 46 countries in different brand names [1].

THALIDOMIDE DISASTER
For its effectiveness in morning sickness in pregnant women Thalidomide was widespread used in different countries. Thalidomide became one of the large selling drugs worldwide. Physicians had been given with sample packets of the drug and had distributed the drug freely to the patients suffering from morning sickness. Soon after the release of Thalidomide, patients complained of peripheral neuropathy after using it. Couple of years after the use of Thalidomide in Australia, Japan, and Europe, approximately 10,000 children was born with birth defects. Thalidomide use also attributed to congenital heart disease, phocomelia, ocular abnormalities and malformation of the inner and outer ear due to which it was banned in most of the countries in 1961. Vargesson et al. studied about the history and mechanism of Thalidomide induced teratogenesis. It was reported by the author that survivors of the Thalidomide disaster were severe handicaps; many of them had experienced early onset of age related issues such as osteoarthritis, coronary artery disease (CAD), and joint mobility issues [2].

RE-ENTRY OF THALIDOMIDE
Though the use of Thalidomide was banned in pregnant women in 1960, because of its immuno-modulatory and anti-pyretic properties it has been used in the treatment of erythema nodosum leprosum (ENL), a complication of leprosy. These days Thalidomide is successfully used in treating diseases such as ENL, multiple myeloma, and cancers, as well as HIV, Crohn’s disease and others [3]. The World Health Organization does not recommend the use of this drug still in leprosy for its use in poor medical surveillance area resulted in a number of thalidomide affected children. The U.S Food and Drug Administration in 1998 had given approval for the treatment of leprosy and multiple myeloma. It exhibits its action human diseases that are dependent on angiogenesis by inhibiting the angiogenesis [4].
PHARMACOLOGY OF THALIDOMIDE
The exact mechanism of Thalidomide is unknown. But in vitro studies and preliminary clinical trials suggested that it will suppress the Tumor Necrosis Factor alpha (TNFa) and down modulation and production of selected cell surface adhesion molecules responsible for leukocyte migration. In cancer patients it will act by inhibiting the vascular endothelial growth factor (VEGF) and angiogenesis [5].

Due inhibition of TNFa Thalidomide found to be effective in the treatment of various skin and mucous membrane disorders, graft-versus host disease, Crohn’s disease, human immunodeficiency virus (HIV) complications and in multiple myeloma [6]. Thalidomide is absorbed slowly and the available data suggest that it has higher bioavailability. It reaches maximum plasma concentration within at least 2 h post administration and the plasma protein binding capacity varies with the type of enantiomer. The (R) - enantiomer has 55% and for (S) enantiomer it is 65% of plasma protein binding. Thalidomide is metabolized by liver, excreted renally and the elimination half-life is 6 h. The estimated apparent volume of distribution is 16L [7].

CLINICAL TRIALS OF THALIDOMIDE
Anticancer effect of Thalidomide was studied within months of its report for teratogenicity. The Eastern Cooperative Oncology Group (ECOG) administered thalidomide to 21 patients with 14 types of advanced cancer, at doses ranging from 600 to 2,000 mg/d. Included in the ECOG study were two patients with multiple myeloma. Although no tumor responses were noted, significant subjective palliation of symptoms was seen in seven patients (33%). The researchers also noted that there probably was a slowing of tumor growth in two patients with rapidly progressive disease [8].

Grabstad et al. studied on 71 patients who received treatment with thalidomide for a variety of cancers. Doses ranges were from 300 to 2,000 mg/d. One patient with renal cell carcinoma is reported to have achieved resolution of pulmonary metastases [9]. These two studies, call for further research on Thalidomide.

Use in Multiple Myeloma
Single-Agent Therapy in Relapsed Myeloma: Singhal et al. conducted the trial investigating the thalidomide activity in relapsed myeloma patients. Treatment included oral doses of thalidomide at 200 mg/d initially for 2 weeks, and then escalated by 200 mg/d every 2 weeks, up to a maximum daily dose of 800 mg/d, depending on toxicity. The overall response rate was 32%. Approximately 10% of patients achieved 90% reduction in par protein levels [10].

Combination Therapy in Relapsed Myeloma: Weber et al. conducted a study on 47 patients. 24 of 47 patients (52%) with resistant myeloma responded to the combination of thalidomide and dexamethasone. Single-agent therapy with dexamethasone and thalidomide had previously failed in many (46%) of these patients, suggesting a synergistic effect with this combination [11]. Barlogie et al. used thalidomide in a combination chemotherapy regimen known as DT-PACE (dexamethasone, thalidomide, cisplatin, doxorubicin [Adriamycin], cyclophosphamide, etoposide) for patients with aggressive myeloma and plasma cell leukemia. Responses were observed in four of five patients, including three who achieved a complete response [12].

Previously Untreated Myeloma
Weber et al. conducted a study on 28 patients with previously untreated multiple myeloma. They were treated with thalidomide dose ranged from 100 to 200 mg orally (PO) at bedtime with serial increments of 50 to 100 mg at weekly intervals, as tolerated to a maximum of 600 mg PO qhs. The response rate was 36%. The median time to remission was 4.2 months [13].

USE IN OTHER HEMATOLOGICAL CANCERS
Macroglobulinemia
Dimopoulos et al. performed a phase II clinical trial with 20 Waldenstrom’s Macroglobulinemia patients. The drug was started at a dose of 200 mg/day with dose escalation as tolerated to a final dose of
600 mg/day. Five patients experienced a partial response after treatment [14].

**Myelofibrosis with Myeloid Metaplasia**
Mesa et al. investigated the impact and tolerability of low dose thalidomide and prednisone in patients with MMM. 21 patients received thalidomide at a dose of 50 mg/day as well as 3-month oral prednisone. Thalidomide and prednisone were well tolerated and 13 patients (62%) responded. Among 10 transfusion-dependent patients seven improved and four became transfusion-independent; six of eight patients with thrombocytopenia achieved a ≥50% increase in their platelet count; four of 21 patients achieved a spleen reduction by >50%. Low doses of thalidomide and prednisone seem to be better tolerated, improving in parallel the therapeutic outcome. Thalidomide and prednisone require further evaluation in earlier stages of MMM. This combination is a reasonable therapeutic choice for patients with MMM whose main manifestation is cytopenia [15].

**Acute Myeloid Leukemia**
A recently reported trial of thalidomide in 16 patients with refractory or relapsed AML showed one complete response lasting 36 months and a transient reduction in marrow blasts in two additional patients. There was no correlation between reduction in levels of angiogenesis and response. Thus, administration of thalidomide in AML is not recommended outside the context of clinical trials [16].

**BENEFITS OF THALIDOMIDE THERAPY**
Thalidomide is an attractive candidate for use in maintenance situations, particularly after high-dose therapy. Thalidomide can benefit patients who do not have a deletion of chromosome 13. The combination drugs are reported to induce a high complete response rate. Reserving the use of low-dose thalidomide for maintenance after transplantation is an effective way of treatment: toxicity is acceptable, drug resistance at time of relapse is not observed, and survival is improved [17].

Spencer et al. in his study “Consolidation Therapy with Low-Dose Thalidomide and Prednisolone Prolongs the Survival of Multiple Myeloma Patients Undergoing a Single Autologous Stem-Cell Transplantation Procedure” proves that addition of thalidomide consolidation following ASCT would improve the overall survival of the patient [18].

**ADVERSE DRUG REACTIONS OF THALIDOMIDE**
Thalidomide is well known for causing adverse reactions (ADRs) to the developing embryo. Since the release of the drug it has been known that Thalidomide will cause peripheral neuropathy in adults on long term use [7]. This is especially seen in patients using Thalidomide for leprosy or multiple myeloma. It can also causes constipation, dizziness, skin rashes in some patients, and drowsiness. Caro et al. reported about the ADRs caused by Thalidomide in multiple myeloma patients. In this study the incidence of ADR was 83.3%. According to this study most common ADR was neurotoxicity (64.71%), followed by blood disorders (17.64%), edema (11.76%) and digestive disorders (5.88%). Almost half of the patients had severe ADR and in almost 17.65% of cases were not resolved [20]. It was reported that ADRs of Thalidomide develops within the first month of therapy mostly at a dose of 400 mg/day. Peripheral neuropathy has been associated with long term use of the drug (>10 months). The severity of the disease varied from mild to moderate. Common side effects were dose-dependent constipation, sedation, ankle edema, dose-dependent dryness of mouth and skin, occurrence of infections, nausea, vomiting and peripheral neuropathy [21,22].

**MONITORING OF RESPONSE TO THALIDOMIDE THERAPY**
Serum/urine electrophoresis for M (monoclonal) proteins, bone marrow biopsy and b2 macroglobulin are routinely used to assess response to therapy. Hemoglobin, total leucocyte count, absolute neutrophil count, platelet count, total protein, serum globulins and serum albumin improves within 2 months of the start of the thalidomide therapy. These parameters are also useful in evaluating the effect of thalidomide [23].
CONCLUSION
Though Thalidomide causes severe adverse effects, the drug has been found to be effective in the treatment of leprosy and multiple myeloma. These days thalidomide has been successfully used in cancer patents and patients with leprosy with promising results.

ABBREVIATIONS
CAD: coronary artery disease, ENL: erythema nodosum leprosum, TNFa: tumor necrosis factor alpha, ECOG: Eastern Cooperative Oncology Group, AML: acute myeloid leukemia, ABBREVIATIONS

REFERENCES
7. https://www.drugbank.ca/drugs/DB01041


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