Thalidomide-An Overview and the Species-Specific Teratogenicity

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Abstract

Thalidomide (TD) is the drug in clinical use since over half a century for variable indications such as Leprosy. In the 1960s, the use of TD leads to the birth of about 10,000 babies with phocomelia. Later on, TD was removed from the market. In spite of Thalidomide Embryopathy (TE), this drug has recently been approved for the treatment of multiple myeloma for specific indications. Species resistance to develop limb deformities was the main reason for its unrecognized teratogenicity during preclinical toxicity testing. The purpose of this review is to discuss the brief history of this drug and the current discovery of a possible mechanism of species-specificity of TE involving SALL4 degradation by Thalidomide-Cereblon (TD-CRBN) complex.

Keywords: Thalidomide; Multiple myeloma; Teratogenicity; Bioavailability; Tranquilizer; Anxiety; Hyperthyroidism; Tuberculosis

Abbreviations: TD: Thalidomide; TE: Thalidomide Embryopathy; CRBN: Cereblon; TS: Thalidomide Syndrome; NO: Nitrous Oxide; ROS: Reactive Oxygen Species; ENL: Erythema Nodosum Leprosum; TNF-α: Tumor Necrosis Factor-alpha; hiPSCs: human-induced Pluripotent Stem Cells

Introduction

Thalidomide (TD) is a white, crystalline, odorless and tasteless powder in its physical characteristics [1]. It was marketed in the 1950s with the trade names as Distaval (UK), Contergan (Germany), Thalomid (Canada) and many others. Currently, this drug is available under the name "Thalidomide Celgene 50 mg Hard Capsules" as the first line treatment of multiple myeloma [7]. TD is available only in the oral form, dose range being 200-800 mg/kg [7].

Pharmacokinetics of TD is the same in the healthy and the patient population [8]. It is slowly absorbed, maximum plasma concentration is reached in 1-5 hours, bioavailability is 90% and has a half-life of 6 hours [8]. TD is present in the plasma as a racemic mixture of the (+)-R and (-)-S enantiomers (Figure 1) [9]. R and S enantiomers are the chemical compounds that are the mirror image to each other and may have different active properties. The racemic mixture is the one having both R and S enantiomers. R or the Right enantiomer is identified as the isomer that rotates the polarized right to the right and the S to the left, thus they are called + and - isomers [10]. The R-isomer of TD has sleep-inducing properties and is 55% plasma protein bound while the S-isomer is teratogenic with 65% plasma binding [7]. R-isomer, with useful properties, was tried to isolate and purify it as a drug but TD turns into a racemic mixture as it enters into the human plasma [8]. Knoche et al. [11], found that human serum albumin influences the racemization process therefore, even purified TD would be converted into both isomers in the human plasma and become teratogenic.
The pharmacokinetics of TD is not altered by age, gender, smoking, and the presence of food in the stomach [8]. No lethal dose has been identified and no antidote is available in case of overdose [1]. TD is not metabolized in the liver and the main route of excretion is through kidneys >90% in the hydrolytic form [7].

History of TD

TD was originally developed by Swiss pharmaceutical company Ciba AG (now part of Novartis) as a tranquilizer in 1952 [1]. In 1954, the German company, Chemie Grünenthal, re-synthesized TD, got 20 years patent and started the clinical trials [2]. TD turned out to be very good sleep inducer, well-tolerated, non-habit-forming and safe drug as over-doses did not cause any adverse event. At that point, TD was being appreciated as a safe sedative without any risk of the accidental death as of barbiturates [1]. According to the information leaflet printed with the drug in August 1956, the drug was highly effective for the treatment of the conditions as: irritability, weak concentration, post-menopausal symptoms, fear of examination, functional disorders of the stomach and gallbladder, febrile infectious diseases, mild depression, anxiety, hyperthyroidism, and tuberculosis. It was claimed that the drug with such high potency, had no lethal dose determined, no side effects and completely safe to be used. Therefore, it became freely available in West Germany [2].

Cheminie Grünenthal researchers found the drug very effective for alleviating morning sickness in pregnant women [1]. As it was believed by the researchers that no drug could cross the placenta and harm the fetus, Chemie Grünenthal aggressively marketed the drug for the treatment of morning sickness. In 1957, TD became available over-the-counter in West Germany and soon it became a drug of choice for the pregnant women [12,13]. At that time, the drugs were not tested in pregnant animals, therefore, TD was not tested too for any teratogenic effects [12]. By mid-1950s, 14 pharmaceutical companies were marketing TD in 46 countries under 37 different trade names except for North America [1].

Recognition of TD teratogenicity

In 1959, an increasing number of phocomelia cases were seen in Germany [2]. McBride [14], an Australian obstetrician, wrote a warning letter to the medical journal, Lancet, after noticing a rare birth defect involving shortened or absent limbs in the babies of the mothers who had used TD during pregnancy. McBride observed, as mentioned in his letter, about a 20% increase in the newborns with phocomelia [14]. He convinced the Crown St. Women’s Hospital in Sydney, Australia, where he was practicing, to stop using the drug ‘Distaval’ and wrote to Distillers, the company responsible for its availability in Australia [12].

Although an increasing number of newborns with limb deformities were being reported in 1959, it was in 1961 when Widukind Lenz, a German pediatrician, and medical geneticist, clearly recognized and indicated the association between TD and the birth of these babies in the areas of Germany where TD was freely available [15]. The observations of McBride and Lenz concerning the teratogenic effects of TD saved countless babies from being the victim of the TD tragedy in the times to come. The drug was taken off from the market in November 1961 [16].

World-Wide Effect of TD

The total estimate of the babies born with phocomelia after TD exposure all around the world was around 10,000 [16]. Reported cases of TD cases were just the minimum estimates all over the world. Stillbirths, early deaths, and babies with minor anomalies were overlooked and not recorded [2]. Lenz, 1988 compiled the data of the reported cases all over the world. According to his estimates, the mortality of TD affected newborns was 40% and the survived cases of 3,900 make 60% of the original total of 5,850 [2].
Germany

In Germany, TD was sold from November 1957 to November 1961 and the affected babies were still being reported by 1964 [15]. The total amount of the drug sold was 30,201 kg over this time period. The exact number of calculated cases of TE was 3,029 [2,15]. The sharp fall in the TD cases was seen after the drug was taken off the market in November 1961 [16]. However, the abnormal babies were born by August 1962 to the mothers who last took the drug in November 1961 [16]. Overall, it was estimated that only in Germany, 5000-7000 cases of phocomelia were seen [16].

Spain

Unfortunately, TD was available in Spain by 1980s. The pharmaceutical company in Madrid failed to warn the Spanish doctors about the teratogenicity of TD. Moreover, the state controls the drug available to the public were really poor. According to the Spanish advocacy group for victims of TD, there were around 300 TD survivors in Spain [17].

UK

In the UK, TD was licensed in 1958 and marketed by the pharmaceutical company Distillers Biochemical Chemical Ltd under the tradename of Distaval [18]. After Germany, the UK was the second bigger user of TD resulting in the birth of around 2,000 babies. While the death toll remained high, Lenz, 1988 collected the files of cases all over the world and reported 400 surviving cases from UK [2]. The drug was removed from the UK market in 1961 leaving 466 TD survivors as of 2010 [18].

USA

The number of TD babies in the USA was seventeen as compared to the huge number of about 10,000 in 46 countries all over the world [13]. The FDA reviewer, Frances Kathleen Oldham Kelsey, for the application of the new drug, TD approval submitted by the pharmaceutical company, Richardson-Merrell, was not satisfied with the data submitted about chronic toxicity studies. As it was stated by the drug manufacturers that no lethal dose could be determined, Kelsey was concerned that if enormous doses were given, there might be some change in the absorption and excretion of the drug and consequently adverse effects. Meanwhile, the British Medical Journal published a letter from a physician, Leslie Florence, reporting peripheral neuritis in patients taking TD over the long period. Kelsey persuaded Richardson-Merrell to submit further data on this serious side effect [13].

A newly discovered FDA memorandum indicates that Chemie Grünenthal approached Smith, Kline, and French (SKF), now GlaxoSmithKline (GSK) for licensing purposes of TD in the USA. GSK conducted animal tests and ran a clinical trial of the drug in the US on 875 people, including pregnant women. It was noted that even in very high doses TD could not induce sleep in mice and no “sleep-inducing” hypnotic effect in experimental animals similar to those observed in humans [13]. SKF declined to commercialize the drug and then Chemie Grünenthal in September 1960, contacted William S Merrell Company and National Drug Company (later Richardson-Merrell, now part of Sanofi). Richardson-Merrell submitted a New Drug Application (NDA) to the U.S. FDA (United States Food and Drug Administration) [1]. The company demanded approval six times and was refused each time by the FDA reviewer, Frances Kathleen Oldham Kelsey [13].

Kelsey’s skepticism about TD limited the damage by the drug in the USA [13]. President John F. Kennedy, on August 07, 1962, presented Kelsey’ the medal for Distinguished Federal Civilian Service which is the highest civilian honor that can be awarded to a U.S. civilian [13].

Canada

TD was sold in Canada under the trade name ‘Talimol’ [19]. The sales period of TD in Canada was from April 01, 1961 to March 02, 1962 [19]. The detailed epidemiological data of the affected babies were reported by Webb in 1963 as the total number of cases being 115. Out of 115 babies, 74 remained alive, 41 died (35%).

TD survivors in Canada had the bilateral limb involvement with affected upper limbs in 42 and both upper and lower limb in 41 [19]. The Thalidomide Victims Association of Canada (TVAC), founded in 1988, is a group of Canadian TD survivors. TVAC promotes awareness about the teratogenic potential of drugs, keeps the public updated on the devastating effects of TD and showcases the work of TD survivors [20]. After TD tragedy, the importance and need of research in teratology and toxicology was realized in the scientific community leading to the formation of toxicology research groups. The Canadian Association for Research in Toxicology (CART) was formed in 1965 and its first formal, annual symposium was held in 1967, entitled “Perinatal Pharmacology and Toxicology”. The society has changed its title to the present day as the Society of Toxicology of Canada (STC) and played a distinct role in shaping the toxicology as a distinct discipline in Canada [21].

Adverse Effects of TD

TD has systemic adverse effects and profound teratogenicity. The teratogenic potential of TD results in TE consisting of Phocomelia and the birth defects in other organs [3].

Thalidomide Embryopathy (TE)

TD sensitivity periods: During pregnancy, the early phase of embryonic development is the period of rapid cell division, growth and movement. This period is a time-sensitive window known as a critical period and lasts until week 10-11. The critical period extends between 34-50 days after last menstrual period. During this period organogenesis, angiogenesis and organ development occurs along with the expression of many different signaling pathways [2,3,15]. Evidence suggests that during the time-sensitive period, a single 50 mg tablet was sufficient to cause birth defects in up to 50% of pregnancies [2,15]. The time-sensitive window of TD teratogenicity was determined after the interviews with the mothers of the affected children and their doctors with very much precision. A precise association was

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found between the time of drug ingested and the organs affected such as eyes and ears (34-38 days), upper limb (38-47 days) and lower limbs (41-48 days) [3,22].

**Embryopathy or syndrome:** TD exposure during pregnancy results in a wide range of birth defects involving multiple organs and systems such as limbs, face, eyes, ears, genitalia, and internal organs, including heart, kidney, and gastrointestinal tract. The whole spectrum of these defects is collectively known as TE or Thalidomide Syndrome (TS) [3]. Eye defects include small eyes (microphthalmia), the absence of the eyeball (anophthalmos) and defects in the lens, iris, or retina (coloboma) [3]. The ear defects range from the complete absence of the pinna or external ear (anotia) to underdeveloped outer ear (microtia). Eye abnormalities may be associated with poor vision and ear anomalies with deafness (Figure 2) [3,16,23].

**Figure 2:** Thalidomide embryopathy hallmarks indicated with a time-sensitive period. Each malformation specifically appears in defined post-conception/post-menstrual days depending upon the stage of embryo growth followed by thalidomide exposure.

Exposure after the time-sensitive period still adversely affects the angiogenesis in the brain and results in the damage to the brain areas causing autism and epilepsy in later life [24].

**Mechanism of action in embryopathy**

The proposed mechanisms of TD teratogenicity include apoptosis or cell death through Reactive Oxygen Species (ROS) [25], inhibition of Nitrous Oxide (NO) in endothelial cells [26] and most recently degradation of SALL4 transcription factor by binding to the Cullin 4 (CUL4)-CRBN E3 ubiquitin ligase complex [27].

**SALL4 degradation via CRBN binding and species specificity**

SALL4 (spalt-like transcription factor 4) is a transcription factor essential for limb development and its heterozygous loss during human development results in phenocopies of TD-like features such as phocomelia, thumbs, ear, eye and heart defects [28]. Recently, Donoven et al. [28] have shown that TD degrades SALL4 in humans, primates, and rabbits indicating a possible mechanism of action for TD. On the other hand, TD had no effect on SALL4 in rodents or fish demonstrating the species-specific and possibly the mechanism of TD teratogenicity [28]. CRBN is a protein encoded by the CRBN gene and plays an important role in embryo development as it forms a ligase complex with other proteins and targets developmentally important transcription factors [29]. TD makes a complex with CRBN which is the component of CUL4-CRBN complex. TD-CRBN-CUL4 complex degrades the SALL4 transcription factor in human cells and rabbits but not in resistant species as mice (Figure 3) [27,28]. It is proposed that the sequence differences in SALL4 between susceptible species, human and rabbit and, resistant species i.e., the mouse is responsible for the degradation of SALL4 by TD-CRBN-CUL4 complex [30]. The currently proposed mechanism of TD teratogenicity is supported by the striking resemblance between TE and the congenital syndromes, Duane Radial Ray and Holt-Oram, which result from the mutation of the SALL4 gene [31]. The investigation into the species-specific differences dates back when Fratta et al. [32] investigated the teratogenic effect of oral administration of TD on rabbits, rats, hamsters and mice and found that the rabbits were the only species that showed the dose-dependent fetal anomalies in the tissues of mesodermal origin such as pes valgus, syndactyly and polydactyly [32]. Recent advances would help to answer the species-specificity of TD-induced birth defects.
Figure 3: Mechanism of species-specific thalidomide teratogenicity. Cereblon (CRBN) is a protein that plays an important role in embryo development. Thalidomide and Cereblon complex degrades the SALL4 (spalt-like transcription factor 4), a transcription factor essential for limb development in Rabbit and human, susceptible species but not in mouse, thus mouse being resistant species for developmental limb deformity.

Vascular and limb development in the embryo

The limb defects caused by TD are considered due to the destruction of the mesenchymal cells and/or the inhibition of the blood vessels growth [24].

The musculoskeletal system including cartilage and bone as well as blood vessels originates from the mesenchyme which is derived from the mesoderm [33]. Blood vessels are essential in order to supply the oxygen and nutrients to the growing tissues, thus essential for the normal embryonic development. There are two main steps in blood vessel development: vasculogenesis and angiogenesis. Vasculogenesis is the first step where a primitive capillary bed is formed from the endothelial cells that have differentiated from mesenchymal precursors. During the step of angiogenesis, the complex blood vessel networks are formed by the process of sprouting. There is a delicate balance between vasculogenesis and angiogenesis during limb development [24,34].

Limb development and blood vessels growth occur at the same time as limb enlarges in the developing embryo [33]. The rapontos et al. [35] have established that out-growth and remodeling of mature blood vessels were blocked while newly developing blood vessels were completely lost or regress after TD exposure in chick embryo model [35]. Moreover, it has also been demonstrated that TD affects in a time-sensitive manner on the chick embryo on the limb development through inhibition of angiogenesis and early exposure results in truncated limbs while the later exposure causes less severe damage, such as loss of a digit or digit tips only [24], simulating the limb defects in human embryos. The proposed mechanism of TD anti-angiogenesis effect is through inhibition of NO in endothelial cells. NO regulates endothelial cells migration and proliferation [26]. TD also causes increased free radical production in rabbit limbs. In addition to direct cell death due to ROS production, TD inhibits the binding of NFkB, a transcription factor that stimulates the FGF-10 expression [25].

In vitro model

The animal models have been used to investigate the TD teratogenicity but the limitation of species-specific differences is a huge barrier to translate the results to the human species itself. Therefore, in order to establish a human-specific in vitro study model Tachikawa et al. [36] used human induced Pluriotent Stem Cells (hiPSCs) to investigate the effect of TD. The study of TD exposure during hiPSC differentiation is equivalent to the exposure of the drug at the stages of epiblast (future fetus) and trophoblast (future extra-embryonic tissue) differentiation [36]. As the effect of TD was detected by the reduction in the number of undifferentiated cells, therefore the model of hiPSCs was validated as an experimental setting to study the teratogenic mechanisms of TD on human embryonic tissues in the laboratory setting [36]. Tachikawa et al. [37] further studied the effect of TD on the differentiation of hiPSCs to the early mesoderm cells. The number of apoptotic and dead cells were increased in early differentiated as compared to the well-differentiated mesoderm cells confirming the association among the time-sensitive exposure of TD, early cell death and embryopathy [37].

Phocomelia

The word “phocomelia” means seal limbs and the term was first used by a French anatomist Etienne Geoffroy Saint-Hilaire for the flipper-like limbs [38]. Limbs and bone defects are the most striking component of TE. The condition involving malformations of arms and legs is known as phocomelia. Phocomelia is characterized by the severe shortening of the limbs where long bones are reduced or missing and distal elements or hand-plates remain with further anomalies [16,24].
Majority of TD survivors have some form of limb deformity ranging from phocomelia to just thumb defect [16]. Limb deformities are symmetrical and appear in a characteristic pattern [2]. Unilateral limb damage is not considered the part of the TS [24]. The upper limbs are not completely developed with flipper-like limbs and missing parts of arm, forearm or hand. In order of preference, the thumb is affected first, followed by the radius, humerus and lastly the ulna. There may be fused fingers, missing thumbs or polydactyly [16,24]. Lower limb defects may show the anomalies with absent pelvic bones, the femur is the most common absent bone and the feet attached close to the body seem like stumps. The fibula is the last bone to be affected in the lower limb [24]. Typical facial anomalies may be present such as a large naevus at birth from the center of the forehead extending down over the nose and upper lip. This capillary haemangioma may or may not be associated with small jaw or micrognathia, cleft palate and cleft lip [16]. The medical conditions that may appear in later lives of TD affection may life include mental retardation, autism, and epilepsy [24]. The other anomalies that may be present as a part of TS include malformations of kidney, heart, genitals, and bowel [16].

**Mechanistic Aspects of Phocomelia in Infants**

Effects of phocomelia on babies, kids, and growing children depend on the extent of the abnormalities in the limbs. These anomalies as assessed by the X-rays of upper and lower limbs can be seen as the absence of humerus and forearm bones in upper limb and femur and leg in lower limbs in a typical case of tetra phocomelia (Figure 4) [39].

The mechanistic issues of the babies and children with phocomelia depend on the location and size of the reduction i.e., whether the upper limb is involved or lower limb and to what extent. The main locomotor challenges include difficulties with the normal development of motor skills, depending on the assistance with daily activities such as self-care and limited certain movements, sports, or activities. Moreover, potential emotional and social issues because of physical appearance are important as well [40]. Babies having limb deformities are treated with the prosthetics (artificial limbs), orthotics (splints or braces), surgery and rehabilitation (physical or occupational therapy) [40]. The mechanistic issues related to mobility lead to the inability of the babies as they grow to learn skills and move forward in their life, therefore, they are offered the various types of prosthesis customized to the area of the body to be applied [41]. Modern prosthetic limbs are efficient, prepared from modern plastics, lightweight and with a natural look. The recent advancement in the field of prosthetics is the myoelectric limbs that can detect the signals from the nervous system and muscles [42].

Nicholas et al. [41], reviewed the 21 TD affected children with limb prosthesis. This study helped to understand the mechanistic effects, challenges and the physical adaptations of the phocomelia babies as they were growing up. Kids with upper limb deformities were offered prosthetic limbs only if their rudimentary arms were not long enough to grasp objects bilaterally, to reach the mouth, and to be within the field of vision. Such children were encouraged to use their feet to

enable them to acquire the sensory perception of texture, temperature. For normal musculoskeletal growth, the developing baby and the kid depend on the vertical positioning of the spine, correct sitting, standing and walking postures at a normal age. Therefore, the infants were trained to sit at the age of six months and by one year supplied with some kind of legs for the sense of mobility. The lower limb prosthesis was fitted in with shoes as they approached schooling age [41]. Coping with the prosthesis with all four limbs posed mental and physical strain. However, gradual adaptation and support helped the growing infants and children to adapt further [41].

The physical disabilities resulting in the infants with limb deformities change their lifestyle and require them to adjust within their environment. The limitations in activities, being with the prosthesis and the level of the support from the environment all determine the quality of life and the participation of the children with the prosthesis [43].

**Adult life challenges**

The studies examining the TD survivors indicate that the decades of coping with stunted, twisted or missing limbs has led to the greater wear and tear on remaining joints and muscles which has resulted in the premature onset of arthritis and chronic pain [44]. 90% of the physical issues present in TD affected adults are of musculoskeletal origin. The main musculoskeletal issues are the pain, wear, and tear of the joint, damage to the joints and tension in muscles. The stumps of the limbs, limited movement, and mal-aligned joints result in the movements at weird angles resulting in over-use of good limbs. Pain in the neck, back and shoulders and the osteoarthritis of the hip (40%) and knee (60%) joints as well as the degeneration of the intervertebral discs have been found in the follow-up studies of TD survivors. Other health issues indirectly related to the pochemelia are lifestyle issues such as hypertension and obesity. Hypertension is challenging to treat as it is hard to accurately assess the blood pressure due to the absence of limbs while obesity is the outcome of physical immobility [44].

**Current Uses of TD**

Currently, TD has been approved by the FDA for the treatment of Erythema Nodosum Leprosum (ENL), a complication of leprosy (1998) and multiple myeloma [5].

**Leprosy**

Leprosy is a chronic skin disease caused by a Gram-positive, acid-fast bacillus Mycobacterium leprae. Clinically, leprosy has two main presentations, tuberculoid and lepromatous. Tuberculoid leprosy is presented with skin erythroid plaques and sensory or motor nerve dysfunction while lepromatous leprosy is characterized by macrophage skin glomerulata containing bacilli, sensory nerve damage and hands and feet deformities.

Clinical trials have demonstrated that TD is effective in the treatment of ENL. ENL is the Type-2 leprosy immune reaction and the systemic disorder associated with fever, malaise, anorexia, leukocytosis, and anemia along with erythematous painful nodules in the skin and subcutaneous tissue anywhere in the body [45]. According to the WHO report [6], TD can be used for the treatment of ENL reaction with strict precautions [6]. TD has been in use for the treatment of ENL for over 30 years and now two large databases are available of the published literature of the clinical trials [45]. One of the largest such trials was started in 1975 and is still ongoing, have by now 1368 participants of with borderline lepromatous (15%) and lepromatous (85%) leprosy.

Results indicated the complete control of the disease was maintained in 83% of patients over 14 years [45]. There is no bactericidal or bacteriostatic effect of TD on Mycobacterium leprae [45]. TD’s beneficial action in treating ENL comes from its anti-inflammatory action by selective degradation of mRNA of Tumor Necrosis Factor-alpha (TNF-α) produced by the monocytes [46]. Physiologically, TNF-α controls the inflammatory response by regulating the interleukins therefore, ENL responds very quickly and effectively to TD [24]. Clinically, TD decreases TNF-α levels in ENL patients while reducing the ENL toxic and systemic symptoms including fever, arthralgia, and the painful subcutaneous nodules [46].

TD is predominantly being used in Brazil for the treatment of leprosy as Brazil is the second highest in the world for the list of new cases of leprosy with the prevalence of this disease being 1.27 to 10.2 per 10,000 of the population [47]. In spite of restrictions, 33 new cases of TE emerged between 1969 and 1995 [48]. The total number of pills distributed in Brazil between 2005-2010 were over five million and three new cases of TE emerged were registered by the TE surveillance systems between 2005-2006 in Brazil [49]. System for Thalidomide Education and Prescribing Safety (S.T.E.P.S. (Celgene Corporation, Warren, New Jersey)), a comprehensive program was launched as a requirement by FDA to market TD for the treatment of ENL. The goal is the lowest possible incidence of drug-associated teratogenicity by the approaches including 1) controlled drug access, 2) educating prescribers, pharmacists, and patients; and (3) monitoring compliance. Clinicians, pharmacists, and pharmacies must be registered and comply with patient identification and monitoring criteria. Patient compliance must be assured by periodic pregnancy tests and filling out a confidential survey about contraception practices [50].

**Cancer**

TD Celgene as 50 mg hard capsules is therapeutically indicated in combination with prednisone as the first-line treatment of patients with untreated multiple myeloma, aged ≥ 65 years and ineligible for the high dose chemotherapy [7]. Multiple myelomas is a malignant disorder of mature B-cells that predominantly affects the elderly. TD with its analogs Lenalidomide and pomalidomide have been shown anti-proliferative, anti-angiogenic and immunomodulatory effects against myeloma cells. They carry out their direct effects through decreased production of key pro-survival cytokines such as TNF-α, IL-6, IL-8, and VEGF that favor tumor cell survival and proliferation [51].
In 2006, the FDA granted accelerated approval to TD as the first-line treatment of multiple myeloma [5]. The clinical trial for its approval was conducted by Singhal et al. [52] on 84 patients in total as a single treatment agent with an administered dose of 200-800 mg. The response was assessed by the presence of Bence Jones proteins in serum or urine. Results indicated 90% response in eight patients, 75% in 6 patients and 32% of the total rate of response [52]. Although the common side effects in such patients are constipation, fatigue, and somnolence, only in 10%-15% of patients have been required to discontinue the treatment due to grade 3-4 neuropathy [53]. Other than multiple myeloma, TD has also been tried in the treatment of Kaposi’s sarcoma, renal cell carcinoma and high-grade glioma with promising results [53]. Currently, TD is used for the treatment of several malignant diseases, including myelofibrosis, renal cell cancer, prostate cancer, and Kaposi sarcoma [54].

The anti-tumor effect of TD comes from the combination of immunomodulatory effect, blockade of TNF-α and the anti-angiogenic effect [53]. Tumors depend on the blood vessels for their survival and growth. Anti-angiogenic drugs are not only effective in solid tumors but also blood cancers such as multiple myeloma [55]. D’Amato et al. [34], discovered the anti-angiogenic properties of TD. Oral administration of TD blocked the corneal neovascularization induced by FGF-2 or VEGF in rabbits. Histology showed the tissue was virtually free of inflammatory cells. Therefore, it was argued that the anti-angiogenic effect of TD was not via the TNF-α blockade [46] but due to the direct effect of the drug on newly growing blood vessels [34].

Other Adverse Effects of TD

TD use is associated with several side effects such as somnolence, constipation are the deep vein thrombosis and peripheral neuropathy [54]. Stevens-Johnson syndrome, elevated liver enzymes, malaise, and peripheral edema are less common side effects [56]. According to the available patient data, doses up to 200 mg/day are well-tolerated [56].

Peripheral neuropathy is the serious side effect of TD and presents as numbness, tingling, pain or weakness in the hands and feet. It starts in 80% of patients (grade 1-2) and 3%-5% of patients (grade 3-4) after about 6 months use of the drug. Clinically, TD has been used in the treatment of multiple myeloma as an immunomodulatory drug with or without dexamethasone. Although proved to be very effective, peripheral neuropathy increases many-folds when TD is used in combination with dexamethasone [4,54,56].

Conclusion

It has been six decades that TD was discovered as a sedative and extensively used for morning sickness in pregnant patients. The teratogenicity of this drug resulted in TS with phocomelia and raised fears regarding the safety of pharmaceutical drugs. TD tragedy left thousands of affected babies all over the world. Phocomelia with limb defects led to the continuous investigation by the researchers for its mechanism of action and species-specificity. Current uses of TD in the treatment of leprosy and multiple myeloma indicate the effectiveness of this drug with promising future. As a result, the drug development and approval process were improved all over the world after this historical incidence.

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