The revival of thalidomide: From tragedy to therapy

Despite its tragic history, thalidomide has found its place in the treatment of leprosy, HIV/AIDS, and cancer.

Gerry Greenstone, MD

In the early 1960s the world was shocked by the tragic spectacle of thousands of children born with malformed arms and legs. The image of those children struggling with deformed limbs has been seared into the public imagination. The defects in limbs and other organs were linked to thalidomide, a supposedly safe drug taken by pregnant women for nausea and insomnia.

Thalidomide was marketed in more than 40 countries and in Canada was licensed for prescription use from April 1961 until March 1962. In this country it caused about 115 cases of malformations, although the actual number was probably higher because of spontaneous abortions and stillborns.[1] For decades this drug became a forbidden word as it was banished from the medical armamentarium.

Yet thalidomide has risen from the darkness of unspeakable tragedy. It has made a remarkable comeback and found its way into the current therapeutic formulary, albeit under strict conditions. Thalidomide and its derivatives have been found to affect many cellular processes in such useful ways that they are now indicated for treating several illnesses, including leprosy and multiple myeloma.

This article has been peer reviewed.

Dr Greenstone is family physician who has also worked in consultation pediatrics in Surrey.

Leprosy

The story of thalidomide's revival begins in 1964 with Dr Jacob Sheskin, who was a dermatologist working with leprosy patients in Jerusalem. Sometimes while undergoing treatment such patients develop a painful condition called erythema nodosum leprosum (ENL), which causes diffuse red nodular lesions along with fever, weight loss, arthritis, and general malaise. In order to relieve one such man Dr Sheskin sedated him with some thalidomide and noted a dramatic response after only four tablets. He then treated another six patients with ENL and noted the same dramatic result.[2]

Further studies involving much larger numbers of patients showed significant responses, and the World Health Organization carried out a short-term, double-blind study of male lepromatous patients comparing thalidomide with acetylsalicylic acid (ASA). This study, reported in 1971, showed significant superiority of thalidomide versus ASA in the treatment of skin lesions but minimal efficacy in neural and internal lesions.[3] Further studies also showed some efficacy of thalidomide against Behcet syndrome and graft-versus-host disease.

HIV/AIDS

In 1991 Dr Gilla Kaplan, a researcher at New York's Rockefeller University, demonstrated that thalidomide inhibited an important cytokine called tumor necrosis factor-alpha (TNF-α), which has multiple immunologic functions involving apoptosis, inflammation, tumorigenesis, and viral replication.[4] Since people with HIV/AIDS are known to have elevated levels of TNF-α, this discovery provided a theoretical framework for using thalidomide in this condition.

Further studies showed thalidomide's efficacy against the aphthous ulcers and wasting syndrome of HIV/AIDS at a time when standard therapies were mostly ineffective.[5] This stimulated the growth of "buyers' clubs," groups of people with HIV/AIDS, particularly in New York and California, who organized to import the drug into the country, mostly from South America. By doing this they came into conflict with the US Food and Drug Administration (FDA), which sought to control the supply and distribution of thalidomide in an effort to prevent a repeat of the terrible tragedy of the early 1960s.[6] The main pharmaceutical company involved

with thalidomide was Celgene Corporation, headquartered in New Jersey, which received patent approval to manufacture it in December 1995. While negotiations between the FDA and Celgene continued, there were other striking developments in the research on thalidomide.

Angiogenesis

In 1994 Dr R. D'Amato, working in the lab of Dr Judah Folkman, showed that thalidomide demonstrated anti-angiogenic properties in a rabbit corneal micropocket assay.[7] They inserted pellets containing bFGF (basic fibroblast growth factor, known to stimulate blood vessel growth) into the corneas of anesthetized rabbits, which were then divided into a control group and a thalidomide group. While the control group showed the expected corneal neovascularization, the thalidomide group showed a significant reduction in this phenomenon. Furthermore, by applying other research to their findings they postulated that this anti-angiogenic effect of thalidomide was independent of its ability to downgrade production of TNF-α. They surmised that it was a direct effect of the thalidomide itself.

These findings paralleled Dr Folkman's earlier thesis in 1971 in which he hypothesized that cancer growth required the development of new blood vessels in a process called angiogenesis.[8] He postulated that if a way could be found to shut down this process, the growth of the cancer could be terminated. His idea was not initially accepted by the medical community, perhaps because it was so revolutionary. However, as a protégé of Dr Folkman, Dr D'Amato continued to study the phenomenon of angiogenesis and its relation to tumor growth. He demonstrated experimentally that the combination of thalidomide and sulindac (an anti-inflammatory) inhibited the growth of carcinoma in rabbits by 75%.[9]

Multiple myeloma

In 1997 Dr Ira Wolmer, a cardiologist, was extremely ill with multiple myeloma, an incurable plasma cell cancer, which had failed to respond to usual treatments. His wife contacted Dr Bart Barlogie, who treated Dr Wolmer with thalidomide—but the effort failed. However, another patient with myeloma responded, which encouraged Dr Barlogie's group at the University of Arkansas to set up a trial of therapy with 84 previously treated but refractory multiple myeloma patients. They monitored blood and urine paraprotein levels, bone marrow changes, and clinical response.[10]

Blood and urine paraprotein levels dropped significantly in 32% of patients, which was matched by bone marrow response in 81% of those evaluated. Furthermore, after 12 months of follow-up, "22.5 +/-5% of the 84 patients remained event-free and 58 +/-5% were still alive." These numbers may not sound very impressive until one remembers that refractory multiple myeloma was at that time uniformly fatal in a matter of months. Thus thalidomide was the first chemotherapeutic drug showing activity against myeloma in more than 30 years.[11] This study spurred numerous further trials of thalidomide treatment for multiple myeloma, which showed significant efficacy of the drug against this disease. In addition, thalidomide has been effective in numerous skin conditions such as lichen planus, cutaneous sarcoidosis, prurigo nodularis, and discoid lupus erythematosus.[12]

In 2004 Celgene developed a structural analogue of thalidomide called lenalidomide (Revlimid) with improved antitumor efficacy and a reduced toxicity profile. In addition to multiple myeloma, lenalidomide has also demonstrated clinical efficacy in some types of myelodysplastic syndromes and lymphoma.[13] Other analogues of thalidomide, such as

Continued on page 232

Continued from page 231

pomalidomide (Actimid), are currently being developed with the promise of greater efficacy and, one hopes, fewer side effects.

The production of these drugs has paralleled recent advances in the understanding of cell biology, which has shown that the essence of the cancer cell is the ability to carry out specific processes such as proliferation, apoptosis-avoidance, angiogenesis, migration, and control of the microenvironment. With a greater knowledge of these pathogenic mechanisms scientists have developed many pharmaceutical agents—such as thalidomide and lenalidomide—that act therapeutically at multiple points in the malignancy cascade. Specifically, they can induce malignant cell apoptosis, augment normal cytotoxicity, inhibit cell adhesion, downgrade angiogenesis, and interfere with cancer-promoting cytokines. These actions impede the growth of multiple myeloma cells and inhibit their control of the microenvironment—crucial components of anticancer therapy.[14]

Side effects

In the early 1960s it was observed that thalidomide could cause significant peripheral neuropathy, and while this problem is less with lenalidomide, the latter carries a greater risk of myelosuppression, especially neutropenia and thrombocytopenia. Both drugs can cause significant coagulopathy with deep vein thrombosis, which can be decreased but not eradicated by concomitant use of ASA. Other observed side effects include skin eruptions, diarrhea, joint and limb pain, fatigue, anorexia, muscle cramps, electrolyte imbalance, and secondary infections.[15] But the biggest concern with these drugs is the need to prevent any recurrence of the tragic teratogenicity of the 1960s.

Preventing malformations

When the FDA approved the use of thalidomide for the treatment of ENL in 1998, Celgene Corporation, in conjunction with the FDA, set up the STEPS program (System for Thalidomide Education and Prescribing Safety), which laid out strict terms and conditions for its use in order to prevent a recurrence of congenital malformations.[16]

Under this system all physician prescribers must fill out a registration card, an informed consent form with the patient, and a thalidomide survey form. Detailed information about contraception is provided to both female and male patients and frequent testing and monitoring of patients is mandatory. Female patients must use two methods of contraception beginning 4 weeks before and 4 weeks after therapy with thalidomide. Because of studies showing the presence of thalidomide in semen, male patients must use condoms throughout the course of therapy.

The tragic experience with thalidomide dramatically exposed the danger of using pharmaceutical agents without proper analysis and adequate testing.

In January 2008 Health Canada authorized the use of lenalidomide (Revlimid) for the treatment of deletion 5q myelodysplastic syndrome (5qMDS) and in August 2010 authorized the use of thalidomide (Thalomid) for the treatment of multiple myeloma in patients 65 or over in combination with a chemotherapeutic agent and steroid.[17]

Both Revlimid and Thalomid are only available through a program called RevAid set up by Celgene and Health Canada, which is very similar to the STEPS program in the US. This program is designed to minimize fetal exposure to these drugs and maintain tight control over their use.

Conclusion

The tragic experience with thalidomide dramatically exposed the danger of using pharmaceutical agents without proper analysis and adequate testing. It illustrated very clearly the need for continued monitoring and regulation of drugs, especially those with teratogenic potential. In keeping with this, pharmaceutical companies must be compliant in releasing all data about their drugs, including negative results, and physicians must be willing to reevaluate a drug in the face of significant adverse reactions. If these conditions are met, then even a drug as notorious as thalidomide can find its appropriate place in the medical armamentarium.

References

1. Webb JF. Canadian thalidomide experi-

ence. Can Med Assoc J 1963;89:987-992.
2. Sheskin J. Thalidomide in the treatment of lepra reactions. Clin Pharmacol Ther 1965;6:303-306.
3. Iyer CGS, Languillon J, Ramanujam K, et al. WHO Co-ordinated short-term double-blind trial with thalidomide in the treatment of acute lepra reactions in male lepromatous patients. Bull Wld Hlth Org 1971;45:719-732.
4. Sampaio EP, Sarno EN, Galilly R, et al. Thalidomide selectively inhibits tumor necrosis factor production by stimulated human monocytes. J Exp Med 1991; 173:699-703.
5. Jacobson JM, Greenspan JS, Spritzler J, et al. Thalidomide for the treatment of oral aphthous ulcers in patients with human immunodeficiency virus infection. NIAID AIDS Clinical Trials Group. N Engl J Med 1997;336:1487-1493.
6. Hanna L. Drug watch: Thalidomide's long and winding road. BETA 1998;April:33-35,#42.
7. D'Amato R, Loughnan MS, Flynn E, et al. Thalidomide is an inhibitor of angiogenesis. Proc Nat Acad Sci USA 1994;91: 4082-4085.
8. Folkman J. Tumor angiogenesis: Therapeutic implications. N Engl J Med 1971; 285:1182-1186.
9. Verheul HMW, Panigraphy D, Yuan J, et al. Combination oral antiangiogenic therapy with thalidomide and sulindac inhibits tumour growth in rabbits. Br J Cancer 1999;79:114-118.
10. Singhal S, Mehta J, Desikan R, et al. Antitumor activity of thalidomide in refractory multiple myeloma. N Engl J Med 1999;341:1565-1571.
11. Rajkumar SV. Thalidomide: Tragic past and promising future. Mayo Clin Proc 2004;79:899-903.
12. Wu JJ, Huang DB, Pang KR, et al. Thalidomide: Dermatologic indications, mechanisms of action and side-effects. Br J Dermatol 2005;153:254-273.
13. Shah SR, Tran TM. Lenalidomide in myelodysplastic syndrome and multiple myeloma. Drugs 2007;67:1869-1881.
14. Hideshima T, Anderson KC. Molecular mechanisms of novel therapeutic approaches for multiple myeloma. Nature Rev 2002;2:927-937.
15. Health Canada. Revlimid (lenalidomide) Fact Sheet. Modified November 2009. Accessed 10 December 2010. www .hc- sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/revlimid_fs_fd_111952-eng.php.
16. Zeldis JB, Williams BA, Thomas SD, et al. STEPS: A comprehensive program for controlling and monitoring access to thalidomide. Clin Ther 1999;21:319-330.
17. Health Canada. Revlimid (lenalidomide). Notice of compliance with conditions. Modified January 2008. Accessed 1 December 2010. www.hc-sc.gc.ca/dhp-mps/prodpharma/notices-avis/conditions/revlimid_qn_aa_111952-eng.php.

Eisen wins Exceptional Support Award

Dr Andrew Eisen of Vancouver, BC, received the 2011 Marcel Bertrand Exceptional Support Services Program Award from the ALS Society of Canada (www.als.ca/).

Dr Eisen not only diagnoses many ALS patients, but also offers advice and support to patients and their families. He understands that to a person living with ALS, 24 hours is a long time, and he therefore altered his practice to meet the unique needs of his patients.

The Marcel Bertrand Exceptional Support Services Program Award is given to an individual or group of health-care providers in recognition of an exceptional support service or program designed to enhance quality of life for people with ALS and their families.

Dr Andrew Eisen