

Thyrogen[®] Increasing Patient Compliance: A Case Study

Thyroid cancer presents as a cancerous tumor or growth in the thyroid gland. Although the prognosis for patients is generally good, it is possible for thyroid cancer to recur, even after successful therapy. Therefore, this cancer requires lifelong and effective medical management. Thyrogen[®] is a synthetic hormone supplement that is used in the continuing treatment of thyroid cancer patients.

The thyroid is a butterfly-shaped gland in the neck with two types of cells that make thyroid hormones. The function of the thyroid gland is to take iodine and convert it into the following thyroid hormones: triiodothyronine (T3) and thyroxine (T4). When the levels of T3 and T4 drop too low, the pituitary gland produces thyroid stimulating hormone (TSH). This stimulates the thyroid gland to produce more T3 and T4.

Thyrogen[®] is an exogenous source of human TSH that is used as an adjuvant treatment during cancer diagnostic protocols to detect recurring or remaining thyroid cancer cells in patients with a history of thyroid cancer. This treatment provides an alternative to thyroid hormone withdrawal for follow up and management of thyroid cancer. Thyrogen[®] reduces the side effects associated with thyroid cancer monitoring and therefore protects patients because they comply with preventive examinations.

Epidemiological Features of Thyroid Cancer

Although thyroid cancer has a relatively high treatment success rate, cancer recurrences resulting in mortality are still a concern. Thyroid cancer occurs more often in women than men. The average age at diagnosis is 45 years old. The American Cancer Society estimates that there will be 23,600 new cases of thyroid cancer in 2004 in the US.ⁱ The number of new cases of thyroid cancer is increasing at 3% per year and as many as 30% of patients with follicular thyroid cancer will experience a recurrence even decades after initial treatment and remission.

Women	Men	2004 (USA)
17,640	5,960	New Thyroid Cancer Cases (Incidence)
1,460	1,101	Est. Thyroid Mortality

Management of Thyroid Cancer

Treatments for thyroid cancer include surgery, radioactive iodine therapy, external beam radiation therapy, and chemotherapy. Typically, the thyroid

gland is removed and then patients are placed on synthetic thyroid hormone supplements. Thereafter, patients are followed for cancer recurrence or remnants of cancer using thyroglobulin (Tg) testing while they remain on thyroid hormone suppressive therapy. Additionally, patients may be monitored using Tg testing and radioiodine imaging after thyroid hormone withdrawal.

Before Thyrogen[®] entered the market, thyroid cancer patients had to experience withdrawal symptoms for up to six weeks when taken off of hormone supplements before undergoing diagnostic testing for recurring cancer. During this hiatus, patients experienced fatigue, weight gain, constipation, mental dullness, lethargy, depression and other adverse reactions. These reactions negatively impact patients' quality of life to such an extent that they often neglect important annual follow up examinations for recurring cancer. Thyrogen[®] allows patients to avoid the symptoms associated with the withdrawal of hormone therapy. This encourages patient compliance with medical follow up.

Development of Thyrogen[®]

Role of NIH

The ability of TSH to stimulate iodine uptake by thyroid cells has been clinically utilized to enhance the detection and treatment of thyroid cancer. Bovine TSH had been a source of exogenous TSH for thyroid cancer treatment in the 1950's.ⁱⁱ However, due to adverse immunological consequences, the clinical use of it declined. A second source of TSH for thyroid cancer was human tissue, but contamination and virus susceptibility was high. There also was a lack of purified human TSH to treat thyroid cancer patients. Because the use of recombinant human TSH would have reduced risk of human tissue-

R & D TIMELINE

Bovine TSH for treatment of thyroid cancer – 1953

Bovine TSH reported to cause resistance and allergic reactions – 1961

TSH obtained from human pituitary glands – 1965

TSH from pituitary glands increased risk for virus – 1974

Induction of hypothyroidism becomes standard method for thyroid cancer diagnosis and therapy - 1978

Isolation and characterization of human TSH gene by NIH scientists and CRADA agreement with Genzyme - 1987

Genzyme licensed to use NIH intellectual property and Phase I and Phase II clinical trials begin– 1991

Reproducible, large scale manufacturing of human TSH – 1993

FDA requests 2nd round of clinical trials - 1995

FDA approval – 1998

derived pathogen contaminants and reduced adverse immunological side effects, researchers began working to derive this form of TSH.

Scientists at the National Institutes of Health (NIH), National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK) successfully isolated and characterized the genetic material necessary to produce the recombinant human TSH protein. This achievement by NIH scientists permitted the production and continuous supply of this protein to patients who now benefit from an improved therapy.

Role of Technology Transfer

Scientists at Integrated Genetics recognized the importance of this technology and entered into a Cooperative Research and Development Agreement (CRADA) with NIH. The CRADA mechanism allows rapid transfer of scientific innovations and development of biological products used to treat patients. Under this agreement, both parties collaborated to improve upon the findings of the NIDDK scientists.

The cooperative research of NIDDK and Integrated Genetics (now Genzyme Therapeutics) conducted under the CRADA resulted in the derivation of a recombinant form of TSH. The NIH Office of Technology Transfer achieved further development of TSH. Securing patent protection, including benchmarks and milestones for product development in the license used to transfer the technology to Genzyme Therapeutics ensured the appropriate commercialization of this technology. This license provided the company with an incentive to invest significant funds and resources into moving this technology into clinical trials and final preparations for the marketplace.

Role of Genzyme Therapeutics

Genzyme Therapeutics was a suitable industrial partner due to their prior research experience on pituitary proteins. Scientists at Genzyme Therapeutics in collaboration with scientists at NIDDK tackled the difficult tasks of genetically engineering a cell line, and developing a reproducible process for the expression and purification of biologically active recombinant human TSH.ⁱⁱⁱ Cells that were successful in this reproduction were increased in number by culture so that TSH could be harvested and purified. The structure, bioactivity and pharmacokinetics of recombinant TSH were all determined in order to assure safety of human administration.

NIH formally licensed the technology to Genzyme Therapeutics in April 1991, which enabled the company to submit an investigational new drug application with

the Food Drug and Administration (FDA) for approval to begin human testing, and to fund Phase I and Phase II clinical trials in that year. Phase II trials continued the following year. The reproducible large scale manufacturing of the drug was completed in 1993. Validation of the drug manufacturing process was completed in 1995 followed by FDA approval in 1998.

Public Health Benefits

Thyrogen[®] advances the therapy for a growing disease condition that preferentially affects women. The therapy also treats a specialized disease population and thus has been designated an orphan drug.^{iv}

Thyroid cancer patients benefit from Thyrogen[®] because they experience fewer side effects of thyroid hormone withdrawal and comply with the recommended follow up after removal of the cancerous thyroid gland. This monitoring of the recurrence and metastasis of thyroid cancer cells is an extremely important step in battling a disease that has a 30% recurrence rate.

Thyrogen[®] improves detection and treatment of thyroid cancer. The successful development of Thyrogen[®] is another example of NIH resources improving the health care of the public.

ⁱ ACS: What are the key statistics for thyroid cancer? <http://www.cancer.org/> Accessed 8/23/2004

ⁱⁱ Sturgeon CT, et al. Treatment of thyroid cancer metastases with TSH and I¹³¹ during thyroid hormone medication. J Clin Endocrinol Metab 13:1391-1407

ⁱⁱⁱ Cole ES, et al. Recombinant Human Thyroid Stimulating Hormone: Development of a Biotechnology Product for Detection of Metastatic Lesions of Thyroid Carcinoma. Biotechnology (1993) 11: 1014-1023

^{iv} Orphan drugs are intended for use in a rare disease or condition.

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NIH Office of Technology Transfer
6011 Executive Blvd., Suite 325
Rockville, MD 20852
U.S.A.

