The History of Paclitaxel

by

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Abstract

Paclitaxel, also known as taxol, is used in the treatment of patients with many different types of cancer including lung, ovarian and breast cancer as well as Kaposi's sarcoma. The actual discovery and development of this drug, however, has been a difficult and tumultuous journey. In the 1950s, The National Cancer Institute (NCI) created the Cancer Chemotherapy National Service Centre for screening different plants that could yield new, effective compounds in treating cancer. Unfortunately, the search had been largely unfruitful; thousands upon thousands of specimens were evaluated with no substantial leads.

On May 22nd, 1964, the NCI received exciting news when extracts of the bark of the Pacific yew tree demonstrated cytotoxic activity. The NCI continued with the evaluation of the Pacific yew tree, commissioning the isolation of more extracts from these trees. All parts of the tree, including the bark and leaves, were used in the isolation process, but very little of the extract could be procured, further stalling experimental studies.

Ultimately, only 10 grams of the active ingredient was isolated from more than 2,000 pounds of trees. Environmental groups feared that the Pacific yew tree would become extinct due to extensive harvesting since the total synthesis of paclitaxel was likely not economical. Fortunately, in 1990, a semi-synthetic method of generating paclitaxel was established by Horton, which utilized the needles of the more commonly available English yew tree.

Paclitaxel was eventually approved by the Food and Drug Administration (FDA) in 1992 and has since been used extensively in the treatment of cancer patients. The actual discovery and development of this drug are often overlooked, but they remain an important part of the history of medicine as a prime example of serendipity, creativity and perseverance.

Introduction

Paclitaxel, more commonly known as *Taxol*, is used in the treatment of patients with different types of cancer including lung, ovarian, and breast cancer as well as the sarcoma named after the Vienna dermatologist Moritz Kaposi (1837–1902) (Vongpaseuth *et al.,* 2007). Paclitaxel and a similar analogue, docetaxel, belong to a class of compounds known as taxanes, which have been the most effective treatment for breast cancer as well as other types of cancers (Henderson and Bhatia, 2007). It remains one of the most important new anti-cancer drugs to be introduced into clinical practice in the last 20 years (Mooberry, 2007). Paclitaxel has netted annual sales of $1.6 billion in 2000 for Bristol Myers Squibb (BMS) but is now available in various generic forms (Cancer: the generic impact, accessed October. 8th, 2007). In addition to

its therapeutic effects, this drug has garnered many controversies, ranging from the origins of its name to the negative environmental impact of isolating this compound from endangered Pacific yew trees (*Taxus brevifolia*).

According to the general consensus of available literature, "modern" cancer chemotherapy originated with research in gas warfare by the Americans and British during World War II (Goodman and Walsh, 2001). Most of the research at that time focused on alkylating agents (*e.g.*, nitrogen mustards) that bind to DNA to prevent the proliferation of cancerous cells or antimetabolites (*e.g.*, antifolic acids) that slow their metabolism. After World War II, this research became available to the public, and different organizations, such as the Sloan-Kettering Institute and the National Cancer Institute (NCI), were established to better understand the pathogenesis of cancer and screen or evaluate compounds with potential anti-cancer activity. In addition, there was greater public awareness of cancer and, with increasing lobbying power of the American Cancer Society, the NCI budget grew from less than $0.5 million in 1937 to nearly $15 million by 1957.

The Work of the Cancer Chemotherapy National Service Center

In 1955, the NCI established the Cancer Chemotherapy National Service Centre for screening the anti-cancer activity of different compounds submitted from various institutions or companies including the United States Department of Agriculture (USDA) (Goodman and Walsh, 2001). One of the most important functions of the USDA was collecting, identifying, storing, and nurturing various plants that could be introduced as beneficial agents in American agriculture. Under a decree initiated by the US President Harry S. Truman (1884-1972) in 1950, the goal was to identify plants that could be used for synthesizing cortisone; plants that did not yield the product were discarded. Fortunately, some of these plants were saved and were sent to the NCI for screening.

The screening methodology at the NCI changed frequently though (Goodman and Walsh, 2001). In 1962, plant extracts were commonly screened against KB cell culture for determining cytotoxity. To assess anti-cancer activity, these extracts were screened against the L1210 tumor line and two randomly selected tumor systems. By 1966, it was discovered that some systems were naturally sensitive to certain plant constituents, producing many false negative results. By the 1970s, KB cell culture and P388, a new *in vivo* leukemia screen, became the standard assays.

A United States department of Agriculture (USDA) botanist, Arthur Stewart Barclay (b. 1932), along with three graduate students, ventured to Washington and amassed samples from the Pacific Northwest forests including bark from a Pacific yew tree (Goodman and Walsh, 2001). The group travelled to Gifford Pinchot National Forest near Mount St. Helens in August of 1962 (Renneberg, 2007). Apparently, there was no particular reason why Barclay decided to sample this tree since very little was known about it apart from simple taxonomic information. Eventually, extracts of the bark were screened by the NCI and found to be cytotoxic on May 22nd, 1964. Interestingly, at that time, only two published reports addressed the clinical applicability of extracts found in this tree; one study even outright dismissed the tree as a likely candidate for isolating anti-cancer compounds.

The objective, from the perspective of the NCI, was then to isolate the active ingredient from the extracts (Goodman and Walsh, 2001). This task was assigned to Monroe E. Wall's (1916-2002) laboratory at Research Triangle Park in North Carolina. Wall and his colleagues discovered the active ingredient in the Pacific yew tree in September of 1966. These exciting findings were announced at an American Chemical Society meeting in April of 1967. Mansukh Wani, a colleague of Wall, along with other investigators (1971), named the compound "taxol" and published their results in a seminal paper with the elucidation of the chemical structure.

Toxicology Studies

With these promising results, the NCI continued with the evaluation of "taxol" (or paclitaxel), commissioning the isolation of more extracts from Pacific yew trees. Ultimately, only 10 g of the active ingredient was isolated from 2600 lbs of the tree, utilizing all parts of the tree including the bark and leaves. Understandably, there was substantial backlash from environment groups (Goodman and Walsh, 2001). They feared that the Pacific yew tree might become extinct due to extensive harvesting of this tree since the total synthesis of paclitaxel was likely not economical. In addition, this tree grows very slowly so too few naturally-occurring and easily-harvestable trees were available to procure amounts of paclitaxel necessary for treating patients (Theisen, 2001). Guidelines were ultimately established to limit the harvesting of these trees.

These environmental concerns were ultimately dispelled with synthetic means of generating the compound. Robert Holton, a chemistry professor at Florida State University, synthesized paclitaxel from the needles of the English Yew (*Taxus baccata*), a more common conifer native to parts of Europe, northwest Africa, northern Iran, and southwest Asia (Holton *et al.,* 1994). The leaves and needles of this tree contains three times more of the nucleus of the paclitaxel molecule, 10-deacetyl baccatin III, when compared to its Pacific counterpart (Theisen, 2001). Side chains are then added to the nucleus to produce paclitaxel. Typically, this process requires 40 synthetic steps with an overall yield of 2% of the final product (Renneberg, 2007).

Unfortunately, this synthesis was not determined until 1990, and assessment of paclitaxel in the experimental phases was often delayed due to depleting supplies of the compound. NCI had actually, at one point, wanted to abandon the project despite investing over $25 million in evaluating the compound as well as generating new synthetic methods; many other hopeful candidate compounds had been scrapped in favour of paclitaxel (Renneberg, 2007).

The department head at NCI reviewed the existing data, including new findings of the effectiveness of paclitaxel in a separate *in vitro* system, and commenced with turning this compound into a clinically useful drug. In particular, Fuchs and Johnson (1978), two NCI researchers, showed that this compound was effective in leukemic mice. The mechanism of this drug was also determined by Horowitz and her colleagues (1979) at the Albert Einstein College of Medicine in New York. This drug binds tightly to microtubules, preventing their breakdown. This action is particularly detrimental to cancerous cells because they require constant remodeling of their cytoskeleton in order to proliferate.

Animal toxicology studies were completed by June of 1982, and in November, the NCI

applied with the FDA to commence human testing through clinical trials (Goodman and Walsh, 2001). In April of 1984, Phase I clinical trials were initiated; one year later, Phase II trials were planned. The first public report of this compound indicating efficacy was published by Rowinsky *et al.* (1988). The drug demonstrated a beneficial effect in melanoma patients and a remarkable 30% response rate in patients with refractory ovarian cancer.

Because of the practical and financial demands necessary in developing this drug, the NCI needed to partner with a pharmaceutical company. Bristol Myers Squibb was chosen as that company. There was some controversy because this company was granted exclusive rights to this drug despite reports and research of this drug being available in the public domain; the trees needed to isolate the compounds were also situated on federal land (Looting the medicine chest, accessed October 8th, 2007).

More controversy ensued when BMS trademarked "taxol" as the drug name. Critics, including the scientific journal *Nature*, argued that taxol had been used as a generic name for a long time (i.e. in experimental studies) and should not be trademarked (Anon., 1995). BMS officials countered that there could be confusion, leading to decreases in compliance or optimal efficacy in patients. There were Congressional hearings and much public debate. The trademarked name was eventually approved, and paclitaxel became the scientific name of the drug.

In 1991, BMS and the NCI signed a Cooperative Research and Development Agreement to accelerate the production of paclitaxel (Goodman and Walsh, 2001). Finally, on December 29th, 1992, paclitaxel received clearance from the FDA and was approved for treatment in patients with refractory ovarian cancer. This drug was also indicated in refractory breast cancer in 1994.

The price of the drug was also considerably high at the time (Renneberg 2007). There was a substantial uproar because BMS had charged 20 times the cost of the raw product. The company argued that this was necessary to recuperate the $1 billion cost necessary in developing the drug.

Two years later, the use of semi synthetic paclitaxel was evaluated. The European Union recommended the approval of this form of the drug. In 1995, it was approved in the UK. One year later, a landmark study published in the New England Journal of Medicine by McGuire *et al.* (1996) showed that the survival time for women with advanced ovarian cancer increased by over 50% over standard treatment when these patients were given paclitaxel in combination with cisplatin (platinum-based chemotherapeutic drug that crosslink's DNA). The results of these clinical trials and follow-up studies helped demonstrate the efficacy of paclitaxel.

Conclusion

Nowadays, taxanes, namely paclitaxel and docetaxel, are common treatments in many different cancers. The efficacy of paclitaxel has been demonstrated both in continuing experimental studies as well as new or on-going clinical trials. Its applicability in different diseases is also been extensively evaluated.

One significant problem with the formulation is that the drug must be dissolved in a toxic solvent (castor oil), which can cause severe allergic reactions. Paclitaxel must also be administered with special intravenous tubes because the solvent can dissolve plastic tubes normally used to distribute chemotherapeutic agents. Over the years, other formulations (*e.g*., albumin-bound) have been explored to decrease morbidity and mortality, lessen side effects, and reduce the use of these special tubes. Despite its sometimes rocky history, paclitaxel remains one of the most effective compounds in the treatment of cancer and possibly, in the future, the treatment of other diseases. The actual discovery and development of this drug are often overlooked, but they remain an important part of the history of medicine as a prime example of serendipity, creativity and perseverance.

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