

Taxol®: An Example of "Fast-Track" Drug Development

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PMI Proceedings, 1993, pp. 616-21

STARTED WITH REACHING FDA AGREEMENT

INTRODUCTION

Following the signing of a cooperative research and development agreement, (CRADA) between the National Cancer Institute (NCI) and Bristol-Myers Squibb (BMS) in January, 1991, Taxol® (paclitaxel) was made a top priority for development by BMS, with the commitment that a new drug application (NDA) would be submitted within four years. As a consequence of this commitment, it was necessary for BMS to undertake a major effort to develop Taxol®—an anticancer agent that had been called the most important new drug to come along in fifteen years—and necessitated that the drug be developed on a "fast track."

The so-called fast track included not only accelerated time of development, but also accelerated review by the FDA of the NDA. From the signing of the CRADA to submission of the NDA, little more than fifteen months elapsed. Five months after submission of the NDA, the application was reviewed by the Oncology Drugs Advisory Committee and recommended for approval. One month later, in December of 1992, Taxol® was approved for use in patients with metastatic ovarian cancer who had failed first-line or subsequent chemotherapy. First commercial Taxol® shipments began one week after formal approval of the drug.

This presentation will review some of the background for the interest in Taxol®, discuss aspects related to the fast-track development of this agent, and discuss the role played by project management in this overall development process.

BACKGROUND AND EARLY HISTORY

Between 1958 and 1980, the NCI sponsored a program in which extracts of more than 35,000 plant species were evaluated for their ability to terminate the growth of cancer cells in culture. In 1963, as part of this effort, samples of the Pacific yew tree (*Taxus brevifolia*), a scarce and slow-growing evergreen tree found in the old-growth forests of the Pacific northwest, were shown to have significant cell-killing activity. Later that same year, Monroe Wall of the Research Triangle Institute, who was under contract to the NCI, expanded these initial observations to show that an extract of yew bark also killed leukemia cells in culture. Three years later, Wall's group was successful in isolating the active ingredient from the bark and named it "taxol." It was not until 1971, however, that Wall and his colleague, M. Wani, together with H.

Taylor, published the structure of the compound (1). Taxol® was shown to have a very complex molecular structure in which the basic taxane ring system is linked to a rare four-membered oxetan ring and has a side chain esterified at position C-13; this ester side chain is essential for the mechanism of action of Taxol® and for its cytotoxicity (2).

These early accomplishments notwithstanding, the development of Taxol® essentially ceased for a decade. Reasons for this delay included 1) as compared to other agents under development at the time, Taxol® did not appear to have superior antitumor activity; 2) significant problems in developing a suitable clinical formulation were encountered because of the poor water-solubility of Taxol®; 3) great difficulty in obtaining, extracting, and preparing a natural product for large-scale clinical use was anticipated (3).

Interest in Taxol® was renewed in 1979 when Susan Horwitz and colleagues at the Albert Einstein College of Medicine demonstrated that the cytotoxicity of Taxol® was due to unique disruptive effects on microtubule structure and function (4, 5).

Microtubules are cellular components whose principal function is the formation of the "spindle" apparatus which cells must have to undergo mitosis (cell division, the process by which most mammalian cells propagate). In addition, microtubules are used by cells to maintain shape, for motility, for anchorage, and for intracellular transport of various substances (6). Microtubules may also play a pivotal role in the interactions of growth factors with cell-surface receptors and in signal transduction whereby cells are directed to turn off or turn on cell division processes, and thus regulate growth (7-10).

Microtubules are polymers (many molecules bound together) of the protein tubulin that exist in equilibrium with tubulin dimers (two molecules bound together). Taxol® binds preferentially to intact microtubules rather than to the dimers (11). As a consequence, the polymer-dimer equilibrium is shifted toward microtubule formation. This shift towards microtubule formation caused by Taxol® is very unique; other drugs, such as colchicine and the Vinca alkaloids that affect microtubules, induce microtubule disassembly (5, 11-14). As a consequence, Taxol®-treated microtubules are very stable (4, 5, 15); this unusual stability inhibits the normal dynamic reorganization of the microtubule network. Cells treated with Taxol® form unusual bundles of tubulin, and although such cells can enter mitosis, they lack the normal mitotic spindle apparatus (16, 17) and cannot complete cell division.

FURTHER PRECLINICAL DEVELOPMENT OF TAXOL®

* → The decision by the NCI to develop Taxol® further in the late 1970s was based on the new knowledge about its unique mechanism of action (see above) and its broad activity in both mouse tumor and human xenograft (human tumor tissues grafted into mice lacking a functional immune system; thus, the "foreign" human tissue is not rejected) model systems used in the NCI's tumor screening panel (18). Taxol® showed excellent activity against the B16 mouse melanoma, a very resistant model system, and good activity against human mammary, human lung, and human colon xenografts, and against two mouse leukemias.

In addition to the NCI studies, independent investigators showed that Taxol® had substantial activity against human breast cancer xenografts in that

it actually caused tumor shrinkage (19, 20). Activity was also seen against xenografts of human endometrial, brain, ovarian, tongue, and lung tumors. ✖

At the NCI, the preclinical toxicology of Taxol® was evaluated in rodents and dogs (18). As is the case with many anticancer agents, the toxic effects caused by Taxol® were most apparent in tissues with rapid turnover such as bone marrow, lymphatic, gastrointestinal, and reproductive tissues. Damage to nerve, liver, cardiovascular, and kidney tissues was minimal.

Because of the inherent lack of water-solubility of Taxol®, it has been necessary to formulate this agent with Cremophor EL® (polyoxyethylated castor oil). In the dog, administration of this vehicle caused severe hypersensitivity reactions (21). Hypersensitivity reactions were also observed when Taxol® formulated in Cremophor EL® was used in the clinic; these reactions have been attributed to the presence of the Cremophor EL® and have necessitated that the patients receive premedication with antihistamines and steroids.

PHASE I STUDIES

NCI-sponsored Phase I trials of Taxol® using many doses and schedules of administration were begun in 1983 (22-30). Early trials were often discontinued because of a high incidence of hypersensitivity reactions; these discontinuations, in fact, threatened the future development of Taxol®.

In spite of the observed hypersensitivity reactions, in the Phase I studies, the major dose-limiting toxicity was shown to be neutropenia (profound depression of the numbers of a type of white cells in the blood). With cumulative therapy, neurotoxicity became particularly evident (25, 26). In leukemia patients treated with high doses of Taxol®, mucositis was seen as the dose-limiting toxicity (22).

In the Phase I trials, Taxol® exhibited activity in patients with melanoma, non-small cell lung cancer, and heavily pretreated drug-resistant ovarian cancer (31). Despite these observations, however, broad Phase II development was not undertaken because of the severe shortages of the drug, the high frequency of hypersensitivity reactions seen in the Phase I trials, and the concern that Taxol® would be difficult to develop due to the problems anticipated in developing a suitable clinical formulation. Rather, Phase II studies with Taxol® were performed in a limited number of types of cancer patients including those with melanoma, renal, or ovarian cancer.

EARLY PHASE II TRIAL RESULTS

* MOST Imp!

By far the most exciting aspect of the first Phase II trials was the marked activity of Taxol® in patients with advanced ovarian cancer. In a study at the Johns Hopkins Oncology Center, eleven partial responses (PR) and one complete response (CR) were observed out of forty-four assessable patients treated (32). Seven minor responses (MR) were also seen; these patients whose tumors shrank 40-49 percent did not meet the criteria for a PR. In this study, the response rate (CR + PR) of 30 percent was deemed to be high. Noteworthy, along with the high activity of Taxol®, is the fact that most patients had been heavily treated with chemotherapy and/or radiation previously; usually such patients are markedly resistant to chemotherapy. In addition, many responses occurred

in patients who were overtly resistant to treatment with platinum compounds, the recognized agents for use against ovarian cancer. Also, the doses of Taxol® that were used were much lower than those previously shown to be safe for minimally previously treated or new untreated patients; this was necessary because previously treated patients have a much reduced hematologic tolerance to most agents. At the doses used, Taxol® had a very acceptable toxicity profile.

Similar activity was seen in studies done by the Gynecologic Oncology Group (GOG) and at Albert Einstein (33, 34). Complete response rates of 12 percent and overall response (CR + PR) rates of 36 percent were seen in the GOG trial (33); these were in patients who had previously received one platinum-based therapy. In patients who were not considered resistant to platinum therapy, the corresponding figures were 21 percent and 50 percent. In the Albert Einstein study, one CR and five PRs were seen in thirty previously treated patients (34); responders had a median duration of survival of twenty-seven months.

Many patients in the above studies suffered treatment-limiting neutropenia. Accordingly, the ability of granulocyte-colony stimulating factor (G-CSF, an agent that stimulates the production of white blood cells) to ameliorate neutropenia and to allow for increased doses of Taxol® to be used was studied in trials carried out by the NCI Medicine Branch (35-37). In patients treated with the combination of Taxol® and G-CSF, neutropenia was no longer dose limiting; rather, it was peripheral neurotoxicity. However, through the use of G-CSF, significantly greater doses of Taxol® could be administered. Out of fourteen evaluable patients, one CR and four PRs were observed, all of whom were unresponsive to treatment with platinum compounds; five other patients experienced MRs.

In summary, it was this marked activity of Taxol® in patients with ovarian cancer, especially those whose tumors were no longer responding to treatment with platinum-based chemotherapy, that was a major factor in NCI's decision to accelerate the development of Taxol®. Accordingly, NCI decided that Taxol® should be developed via the CRADA mechanism whereby NCI and the development partner share data and coordinate future development efforts. The major initial objectives of the CRADA would be to increase drug supplies in order to allow the NCI to expand greatly the clinical usage of Taxol®, to assure wide commercial distribution of the approved product, and to establish alternative sources of supply (38). In a competitive process, BMS was selected as the CRADA partner, largely based on its experience and success in developing oncologic drugs, its past experience with natural products, and its submission of an aggressive Taxol® development plan. In return for devoting financial and scientific resources and for supplying the drug, BMS was to get exclusive rights to the NCI's clinical trial data. This exclusivity was needed because Taxol® was part of the public domain, and as such was not patentable. The clock started ticking in January of 1991 with the signing of the CRADA between NCI and BMS; the NDA was to be filed by the end of 1995.

Turning points

BMS Partnership with the "RIGHT" Partner.

INITIAL EFFORTS AT BMS

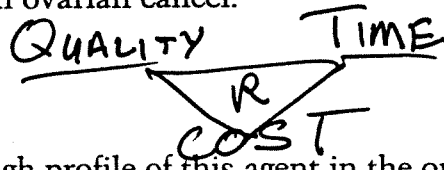
3 TREES
for 1 patient *

A major initial goal was to increase the supply of Taxol® so that the NCI could establish treatment referral centers to provide Taxol® therapy for appropriate ovarian cancer patients until the NDA was approved. The factors to be overcome in increasing the supply of Taxol® stemmed from the fact that the bark of the Pacific yew was the only readily available source of Taxol®. This fact, coupled with the knowledge that about 12,000 women die from ovarian cancer each year in the United States, and the fact that the bark from approximately three trees would be required to treat one patient, emphasized the enormity of the task. Furthermore, at about the same time that the CRADA was signed, data began to appear that showed that Taxol® had excellent activity against breast cancer; thus, the requirements for Taxol® could explode to where more than 300 kilograms of the drug would be needed each year.

Unfortunately, because of the complexity of the Taxol® molecule, complete laboratory synthesis of the drug was not an option at the time; in fact, even now, total synthesis of Taxol® has not been achieved, and it is problematic that such will ever be the case.

In order to increase the supply of Taxol®, agreements were signed between BMS and Hauser Chemical Research of Boulder, Colorado. Hauser and BMS forged agreements with the United States Bureau of Land Management to oversee collection and processing of Pacific yew bark. Even with this agreement, no federally owned lands could be logged beyond those that would normally be slated for logging.

During this collaboration, BMS supplied scientific expertise to Hauser that enabled the partners 1) to double the yield of Taxol® from bark extraction, 2) to exceed NCI's requests and needs for drug supplies by 1991, permitting the establishment of ovarian cancer treatment referral centers, and 3) to increase deliveries to NCI of the drug from 5,000 vials of clinical material per month to 50,000 vials per month in 1992. This permitted the NCI to establish treatment referral centers for patients who have breast cancer (38), a much more common tumor than ovarian cancer.



ROLE OF THE PROJECT DEVELOPMENT TEAM

High Visibility

upper mgmt support!

Given the demand for Taxol® and the high profile of this agent in the oncology community at large, as well as the degree of coverage of the Taxol® story in the lay press, the project development team (PDT) for Taxol® was formally established immediately after the signing of the CRADA. Within BMS, Taxol® was designated as the number one priority agent for drug development. This designation allowed for work on Taxol® to progress at an accelerated pace. Extensive resources were reassigned to the project, and upper management made it known that, above all else, the development of Taxol® would proceed with the greatest possible speed. In fact, rather than a target date for an NDA filing of 1995, this was shortened to 1992. Even though speed was of the essence, however, quality could not be, and was not, sacrificed.

communications opened

It was the purpose and mandate of the PDT to optimize development of Taxol® and, to do so, lines of communication among the various line functions were opened as well as lines of communication to, and from, upper management. PDT meetings were much more than "review of progress" sessions; members of the team became "problem solvers." *

Being a member of the PDT for the number-one agent in the company had both "pros" and "cons." On the positive side, some members of the team found a certain degree of recognition within the company, and hence, a sense of pride developed, not only from a personal point of view, but also from a team aspect. Within their line functions, no major difficulties were encountered in obtaining the resources necessary to perform the required duties; i.e., work on no other project was allowed to supercede work on the Taxol® project. At the same time, there were negative aspects to being a member of the Taxol® PDT. The pressure was intense to get the work done in a timely fashion, but to "do it right the first time." Tempers became short at times because of this; project management played a major role in resolving many of the conflicts that arose (see below).

* Discuss
COMBA,
FATIGUE *

THE PROJECT MANAGER'S ROLE

As mentioned above, an important role for the project manager on the Taxol® PDT was that of arbitrator. As is often the case with a high profile project, stress management becomes a major issue. No time could be wasted by pointing fingers and blaming others. This fact was emphasized as the project progressed in complexity and the target date for the filing of the NDA came ever closer.

Stress
Mgt
as a
major
role!

On occasion, differences of opinion among team members could not be resolved at the PDT meetings since such problems usually were between just two or three line function representatives. In such cases, with the assistance of the project manager, problems could be resolved via teleconference calls.

In other more difficult cases, the project manager would arrange sub-team meetings to discuss the issues in detail. In addition, in the case of Taxol®, face-to-face discussions between the project manager and the various affected team representatives took place. This latter strategy proved to be very effective since PDT members were scattered among various sites within BMS, including research and development sites in New Jersey, New York, and Connecticut. At such face-to-face encounters, the importance of the representative's contributions to the development strategy were reiterated, thus rekindling the "sense of pride" alluded to above.

"MBWA"
Coach &
cheer leader

As the time for the NDA submission drew closer, the project manager's interaction with members of the Regulatory Affairs Department became increasingly frequent. Through this interaction, report submission dates, and so on could be readily monitored, and if major problems were foreseen that could not be resolved at the team level, upper management could be informed without delay, and the solutions could be found at that level.

The project manager's roles during the development of Taxol® were those of project monitor, facilitator, communicator, and peacemaker. Given the high priority of the Taxol® project, these roles were supported by management. In essence, the project manager was given the opportunity to do what had to be done to get the project accomplished.

REGULATORY AFFAIRS AND THE "FAST-TRACK"

A significant factor in the ability to get a rapid review of the Taxol® dossier by the FDA was the fact that regulatory affairs personnel established a good rapport with agency personnel through regular communication throughout the development of Taxol®. This communication not only included BMS personnel,

Relationship
Rapport

but also those from NCI. As part of the CRADA agreement, a joint NCI-BMS steering committee for Taxol® was established. This committee met on a regular basis to discuss all aspects of the drug's development. This committee is still functioning at the present time, and there are no plans to disband it. The close collaboration between the NCI and BMS was best revealed when the NDA was reviewed at the FDA; both NCI and BMS personnel participated in the presentations before the reviewing body. Perhaps the best example of the successes of this collaboration and of the close communications with the FDA was that at the NDA review meeting, it was stated that the Taxol® dossier was the best organized application that the reviewing body had seen, and that it could serve as a "model" for other oncologic drug applications.

It is also apparent, however, that no matter the degree of FDA-company communication, the application would not have been reviewed with the alacrity that it was if Taxol® were not in such great demand, especially by the thousands of patients suffering from essentially untreatable ovarian cancer. The political pressures existing at the time surely played a major role in the agency's rapid review of the Taxol® NDA. However, the application was one of high quality (see above), so the review was no less complete than would have been the usual case.

LIFE AFTER THE NDA APPROVAL

Although Taxol® has been approved for use against ovarian cancer in the United States, Canada, and other countries, much more remains to be done. In addition, to the usual supplementary submissions for other indications, most notably breast cancer, a significant effort is being expended to establish alternative sources (to Pacific yew bark) of Taxol®. Given the concern regarding environmental implications of logging in general, reliance on a single species as a source for the drug would be imprudent. BMS and others are actively engaged in pursuing other avenues for obtaining Taxol®; these include using other yew species where the drug may be obtained from "renewable" parts of the plant, e.g., the needles, and thus the plant would not need to be destroyed. Ornamental cultivars and plant cell cultures are also being examined as possible sources for commercial quantities of the drug. Most promising, however, is the production of Taxol® by semi-synthesis. Here, a precursor of Taxol®, 10-desacetyl-baccatin, which has no antitumor activity in its own right, is chemically converted into Taxol®. The precursor is found in the needles of many yew species worldwide, and since needles are a renewable source, the supplies of 10-desacetyl-baccatin appear inexhaustible. Lastly, a major effort is being directed within BMS and elsewhere towards the discovery of analogs of Taxol® that may not require formulation in Cremophor EL®. Such analogs would not require the pretreatment of patients with antihistamines and steroids, and could prove more advantageous than Taxol® in that they might be more readily administered on an outpatient basis. However, any Taxol® analog would be classified as a new chemical entity distinct from Taxol® and, as such, would require a complete development effort of its own.

All of the projects mentioned above are ongoing, and all require relatively constant monitoring. The sense of urgency felt by the Taxol® PDT at BMS prior to the submission of the original NDA has not abated to any great degree. In concert with this, the role of the project manager in the

Team
collaboration

11 HIGH QUALITY
APPLICATIONS
PLAYED SIGNIFICANT
ROLE!

changing
role
of
PM

overall development of Taxol® has not diminished. In fact, the diversity of Taxol®-related issues appears certain to make the project manager's role ever more interesting and challenging in the years to come.

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1. What was the initial objective(s) of the project? What were the main reasons for the achievement of this objective(s)?
2. BMS and the NCI worked together to get Taxol accepted quickly. How is this stakeholder relationship going to affect the long-term aspects of other related projects?
3. List a few characteristics of the described project manager's role which you would consider important.
4. After the NDA had been passed, how would the project manager's job change?
5. When working on the development of Taxol, how should the project manager have managed and motivated project team members?