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News report

Bristol-Myers Squibb involved in developing alternative sources of TAXOL®

According to the National Cancer Institute (NCI), TAXOL® (paclitaxel) is one of the most important anticancer drugs developed in the past decade. Although significant progress has been made in developing alternative sources of TAXOL, the bark of the Pacific yew tree is currently the only approved source of taxol for human use.

To expedite the development of paclitaxel, NCI signed a Cooperative Research and Development Agreement (CRADA) with Bristol-Myers Squibb Company in January 1991 after a competitive process involving several pharmaceutical companies. The agreement stipulates that, in exchange for exclusive access to NCI clinical and pre-clinical data necessary to file a New Drug Application, the company would supply TAXOL to NCI for clinical research and compassionate use programs, investigate alternative sources of TAXOL and file a New Drug Application as quickly as possible.

TAXOL is an extremely difficult drug to manufacture and its development had been hindered for a number of years by a very limited drug supply. The NCI could manufacture only enough drug to treat several hundred patients a year.

Bristol-Myers Squibb originally projected in 1991 being able to end reliance on Pacific yew bark within 5–8 years. Company officials now report that significant amounts of TAXOL are expected to be produced by semi-synthetic means in 1993 and that Bristol-Myers Squibb expects to eliminate the need for Pacific yew bark completely by no later than the end of 1995—essentially accomplishing this objective in half the time originally anticipated.

The following are specific programs supported by Bristol-Myers Squibb in its comprehensive search for alternative sources.

Semi-synthesis

The most promising alternative source and the alternative expected to produce significant amounts of TAXOL in 1993, is semi-synthesis. This method produces TAXOL from a precursor, 10-deacylbaccatin III (10-DAB), which comes from entirely different yew species, the European *Taxus baccata* and the Himalayan *Taxus wallichiana*.

Bristol-Myers Squibb has reached an agreement with Indena—a company in Milan, Italy which specializes in natural products—under which Indena will extract 10-DAB, the precursor, from the twigs and needles of these trees. As a source of TAXOL, twigs and needles offer a considerable advantage over bark, since they are renewable biomass.

Bristol-Myers Squibb has licensed methods being perfected by Robert Holton, at Florida State University in Tallahassee to convert 10-DAB into paclitaxel and continues to support Dr Holton's research efforts to improve the process further.

Yew cultivation

As indicated above, paclitaxel has been found in other *Taxus* species around the world. Another source under study is development of a domesticated alternative to the wild population Pacific yew through the use of commercial plantations.

Bristol-Myers Squibb signed a 3-year research agreement with Weyerhaeuser Company in August 1991 to determine the best species to cultivate. Methods to enhance the seedlings' growth rate and their content of paclitaxel or a precursor are also being studied. Weyerhaeuser currently has more than 50 000 yew trees in research trials.

Since cultivated biomass is required before this research will be completed, a subsequent agreement was signed for large-scale production of the most promising yew trees. Over 5 million seedlings of a readily available ornamental yew have been planted already and will be ready for harvest in 1994. Weyerhaeuser expects to plant 10 million additional yew trees during 1993. Subsequent crops should be enhanced by results of the research in progress. Investigators at the University of Mississippi's Research Institute of Pharmaceutical Sciences are working under a separate agreement—in collaboration with the Ohio Agricultural Research and Development Center and Zelenka Nursery—to investigate the use of raw materials from ornamental yew nursery stock clippings as a source of TAXOL.

Other research supported by Bristol-Myers Squibb into various ornamental and wild yew species as potential sources of TAXOL includes research at the New York Botanical Garden and the State Pharmaceutical Administration of China.

Plant cell culture

To date, no pharmaceutical products are produced on a commercial scale by plant cell culture techniques. However, researchers have found it possible to grow cells in the laboratory from yew tissues and then to use the cells to produce small quantities of paclitaxel.

Bristol-Myers Squibb is exploring this approach and is encouraged at this early stage by the control, adaptability and potential similarity to well-established fermentation and mammalian cell culture production techniques. Researchers are working to make this process, which is currently very lengthy, commercially feasible.

Bristol-Myers Squibb has established a research and development collaboration with Phyton Catalytic, Inc.—a plant biotechnology company based in Ithaca, NY—to develop a plant cell tissue culture process for the production of paclitaxel. Phyton Catalytic was the first commercial organization to produce paclitaxel in a tissue culture system and has an exclusive license from the US

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Department of Agticulture to produce paclitaxel using this technology.

Bristol-Myers Squibb is also constantly examining research under way at a variety of academic institutions, such as the work being conducted at Pennsylvania State University on the development of improved cell lines for the plants that produce paclitaxel.

Total synthesis

The complexity of the chemical structure of paclitaxel has thus far prevented researchers from totally synthesizing the paclitaxel molecule despite the efforts of many academic laboratories. But researchers are making significant progress and believe total synthesis could someday provide a reliable source of TAXOL that is not dependent on any natural product.

Bristol-Myers Squibb is currently sponsoring well-advanced research at Ohio State University by Dr Leo Paquette and at Stanford University by Dr Paul Wender. The Stanford research team has discovered it is possible to make a core molecule like that found in paclitaxel from a pine tree extract, pinene, which is a major component of industrial solvents such as turpentine and, thus, readily available. Additional work is required to complete this phase of research and to develop it to a level where it will be commercially viable, a process that could take several years.

At Ohio State University, researchers sponsored by Bristol-Myers Squibb began a 2-year research program in August 1991. They are attempting to assemble the framework of the paclitaxel molecule to create synthetic paclitaxel. Although initial progress has been promising, the final stages of the project are still not imminent.

Taxol reported to improve cancer treatment at ASCO meeting

Researchers at the 29th Annual American Society of Clinical Oncology (ASCO) meeting reported improvements in various cancer treatments due to taxol.

With more than 9000 members, ASCO is the largest association of cancer specialists engaged in clinical research and patient care in the US. More than 9000 cancer specialists attended the 1993 ASCO annual meeting, held 16–18 May in Orlando, FL.

Chemotherapy after debulking surgery

Interventional debulking surgery in ovarian cancer patients increases disease-free and overall survival, according to a major study presented at the annual meeting of the ASCO.

Debulking surgery is a technique used almost exclusively with ovarian cancer. It involves removing the majority of the tumor when it cannot be extricated in its entirety. The remaining tumor is then treated with chemotherapy to effectively shrink it. This process is effective in ovarian cancer because, unlike other malignancies, these tumors commonly spread by peritoneal seeding (small 'seeds' fall from the tumor onto intra-abdominal structures). Debulking surgery can be associated with an almost 40% cure rate for ovarian cancer.

"The results of this interventional debulking surgery study will have a major impact on the treatment of ovarian cancer", said Margaret Kemeny, (North Shore University Hospital) at a press briefing on advances in gynecological oncology. "Until now, oncologists could only suggest that a second surgery had positive effects on the survival rates of ovarian cancer patients. Now there is solid evidence to confirm those beliefs, and physicians will likely modify their standards of treatment accordingly".

Led by MEL van der Burg (Rotterdam Cancer Institute) a randomized study of 299 patients with epithelial ovarian cancer compares surgical removal of the primary disease followed by chemotherapy to primary surgery followed by chemotherapy and a second, interventional, surgery followed by a second cycle of chemotherapy. Results after a 30 month mean follow-up period showed that median disease-free survival in patients receiving the second surgery was 15 months, as compared with 12 months in those patients receiving only primary surgery. The median overall survival rate for patients receiving the second surgery is 27 months versus 19 months for the control group.

Granulocyte colony stimulating factor (G-CSF) support with dose-intense taxol shows lack of cumulative bone marrow toxicity

Also promising for the treatment of ovarian cancer are the results from a phase II trial showing that taxol did not cause significant bone marrow toxicity. The combined administration of G-CSF and taxol allowed maintenance of a high-dose intensity of taxol throughout the course of therapy. G-CSF is a substance used in cancer therapy to promote white blood cell growth.

Taxol, one of the newest drugs studied for ovarian cancer, has consistently demonstrated significant antineoplastic activity in patients with advanced metastatic disease. Previous studies indicate that 35% of women afflicted with ovarian cancer responded favorably when treated with taxol.

In the phase II study presented at the annual ASCO meeting by Charles J Link, Jr (National Cancer Institute), 48 patients were administered taxol with G-CSF for 21 days. Patients receiving one dose of taxol with G-CSF showed the same white blood cell counts after one cycle of therapy as after eight cycles. Thus, a depletion of bone marrow was not seen and an increase in the dose of G-CSF was not required.

"Knowing that at least eight cycles of taxol can be administered without cumulative toxicity is a major advance for physicians studying the effects of the drug in ovarian cancer, as well as lung cancer and other malignancies", said Dr Kemeny. "The next step is for researchers to study the effects of maximum doses of taxol".

Peritoneal cancer occurs after prophylactic oophorectomy

Another development in the treatment of ovarian cancer involves the report of the Gilda Radner Familial Ovarian Cancer Registry. The results of this study show that after a prophylactic oophorectomy (surgical removal of the ovaries) six of 324 women with a family history of

ovarian cancer have developed cancer of the peritoneum which is indistinguishable from ovarian cancer. The lead author of the study, M Steven Piver (Roswell Park Cancer Institute), presented the results at the ASCO annual meeting.

"Although the results of this study are disturbing and cause for further evaluation in this population, it is important to recognize that the majority of the women receiving the prophylactic oophorectomy did not develop cancer", noted Dr Kemeny. "The current practice of prophylactic oophorectomies is a valid one that should be continued in women with a family history of ovarian cancer".

Familial ovarian cancer is defined as disease occurrence in two or more first degree (mother, sister, daughter) or second degree (grandmother, aunt, first cousin, granddaughter) relatives. From its initiation in 1981, the Gilda Radner Familial Ovarian Cancer Registry has accessioned 931 families totalling 1221 cases. Examination of the pedigrees is consistent with an autosomal dominant inheritance pattern which means that the dominant distinguishing gene is not carried on the X or Y sex chromosome. Therefore, prophylactic oophorectomy has been recommended for women after aged 35 who have completed their families.

The chances of women with a strong family history of ovarian cancer developing the disease have been reported to be as high as 50%, compared to 1.4% for the general population in the US. In addition, hereditary cancers generally occur in women an average of 10 years earlier than do non-hereditary cancers.

Major study confirms combination therapy for endometrial cancer

A randomized study of 297 endometrial cancer patients conducted by the Gynecologic Oncology Group (GOG) confirmed that combining proven chemotherapeutic agents doxorubicin and cisplatin offers a statistically greater response than using doxorubicin alone. The study was presented at the ASCO annual meeting by lead author, James Tate Thigpen (University of Mississippi School of Medicine).

"While there has been some controversy in the past about the effects of combination therapy on endometrial cancer, these positive results should eradicate any doubt that doxorubicin/cisplatin is an important first-line treatment", said Dr Kemeny.

Endometrial and ovarian cancer statistics

The endometrium or lining of the uterus is the most common site of invasive cancer of the female genital tract and the fourth most frequent site of malignancy in American women. Approximately 31 000 cases of endometrial cancer will be reported this year and it is estimated that the disease will kill 4400 women. Endometrial cancer usually occurs in women past the age of 50 who are at or past menopause. The overall survival rate for endometrial cancer is 89% and 94% if the disease is diagnosed at an early stage.

It is estimated that one out of every 65 women in the US will develop ovarian cancer by the age of 85 and it accounts for 4% of all cancers among women. This year ovarian cancer will be diagnosed in an estimated 22 000 women and 13 300 will die from the disease. Currently, two-thirds of women with ovarian cancer have stage III or stage IV disease at the time of diagnosis. Overall, women with advanced disease have a 5 year survival rate of 39%. In contrast, 75–95% of women with stage I disease can be cured.

Ovarian, breast and brain cancers

Improved clinical response rates and time-to-tumor progression were found in a study using the anti-cancer agent taxol in the initial treatment of ovarian cancer, according to researchers from the GOG, led by William P McGuire (Johns Hopkins University).

This new use of taxol is among several major studies of new cytotoxic agents presented at the meeting. Other chemotherapeutic agents discussed included taxotere, temozolomide and etoposide phosphate.

Results from taxol/cisplatin study may change clinical practice

"It is exciting that the first clinical data for taxol as an initial therapy for the treatment of ovarian cancer are so positive, and it is likely that taxol in combination with cisplatin will soon become front-line therapy for this disease", said Richard Schilsky (University of Chicago) at a press briefing on new cytotoxic agents. "Oncologists have been anxiously awaiting the results from this study".

Results from taxol combined with cisplatin compared with the conventional therapy of cyclophosphamide and cisplatin were gathered from a randomized study of 388 patients with newly diagnosed advanced ovarian cancer. These patients all had residual disease post-surgery measuring greater than 1 cm. The clinical response in 209 evaluable patients was 79% in the taxol arm, compared with 63% in the control group. Additionally, the median duration of time-to-tumor progression for patients receiving taxol (17.9 months) was better than that for patients receiving cyclophosphamide (13.8 months) Dr McGuire also reported that overall survival data are not yet mature enough for definitive conclusions and that the replacement of cyclophosphamide with taxol for the treatment of ovarian cancer was associated with an acceptable toxicity profile.

"The fact that there was a higher rate of negative, second-look laparotomies in the cisplatin/taxol group, raises the possibility that ultimately the use of taxol might result in improved overall survival rates", said Brian Leyland-Jones (McGill University), who also commented on the studies at the ASCO press briefing on new cytotoxic agents. "Additionally, the benefits of increased survival should far outweigh the inconvenience of marginally increased side-effects from the taxol arm, which in further studies will likely be reduced".

Use of taxotere in breast cancer produces significant results

Data from a phase II study of taxotere, a chemotherapeutic agent related to taxol, as initial therapy for advanced breast cancer show a 73% overall response rate, with six patients achieving a complete response, reported Pierre Fumoleau (Centre Rene Gaudechau Nantes-St Herblain, France).

Dr Fumoleau added that 18 of 33 previously untreated patients achieved a partial response with taxotere and five experienced disease stabilization. Four of the patients studied showed progressive disease.

"Preliminary findings from this study establish taxotere as one of the most effective single agents in the treatment of breast cancer", said Dr Schilsky.

Taxotere's side-effects profile was similar to taxol's, except for peripheral edema and/or effusions seen in 12 patients. Dr Fumoleau reported that future studies will investigate the cause of these side-effects.

"In addition to its high level of activity, the exciting potential advantages of taxotere are its possibly unlimited supply and ease of administration", noted Dr Schilsky. "Unlike taxol, pre-medication for allergic reactions is not required with taxotere, and it can be infused in 1 h rather than the standard 24 h period required with taxol".

Major activity seen with new oral agent for brain tumors

Investigators studying a third new cytotoxic agent presented at the meeting reported that the oral agent temozolomide produced a 43% response rate in patients with brain tumors, an exceptionally difficult cancer to treat.

"Brain tumors rarely respond to chemotherapeutic drugs, and any new agent that shows activity as high as 40%, is potentially a breakthrough", said Dr Leyland-Jones. "From the data presented, temozolomide may be one of the most active agents for brain tumors ever reported".

In a phase II study led by Susan M O'Reilly, (Charing Cross Hospital, London), temozolomide was administered to 44 patients, previously untreated with chemotherapy. Sixteen of the patients had received prior radiotherapy and 28 received the drug immediately following surgery. Improvements in computed tomography (CT) scan and neurlogical status were noted in six of the 13 evaluable patients previously treated with radiation; reduction in the size of the CT lesion was observed in 12 of the 28 patients in the second group. Overall, results showed the drug was well tolerated with little toxicity and predictable myelosuppression (depression of white cells).

"The ability to administer temozolomide orally is a major advantage of this drug that may lead to improved quality of life", added Dr Leyland-Jones. "Overall this is very exciting data, and it will be interesting to follow its further study, particularly regarding survival".

Significant benefits derived from new formulation of etoposide

Results from an initial study of the new chemotherapeutic agent etoposide phosphate show potential advantages over etoposide, according to the study's lead author, Daniel R Budman, (North Shore University Hospital, Cornell University Medical College). Etoposide is commonly used to treat lung, lymphoid and testicular cancers.

Etoposide phosphate is a water soluble analog of etoposide that is broken down in the body to produce etoposide. Etoposide phosphate does not have to be diluted with solubilizing agents that may contribute to the toxicity of etoposide and that limit the rate at which etoposide can be safely administered.

Dr Budman reported that etoposide phosphate can be dissolved in standard intravenous solutions and rapidly administered over 5 min. In contrast, etoposide must be given slowly for 45–60 min to minimize acute side-effects, such as shortness of breath, asthma and lowered blood pressure. These side-effects are believed to be related to the solvent. No serious side-effects were seen with patients receiving etoposide phosphate.

"Etoposide phosphate's rapid infusion time and potential for administration at increased doses will probably soon result in the replacement of etoposide for the treatment of solid tumors", said Dr Schilsky. "These benefits also make possible additional studies of the new agent, based on evidence that prolonged use of etoposide may produce more favorable outcomes than current practice".