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Taxane Anticancer Agents

Basic Science and Current Status

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Chapter 3

Current Status of Clinical Trials with Paclitaxel and Docetaxel

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The unique mechanism of action of the antimicrotubule agent paclitaxel suggested that it would be a potent antineoplastic agent. However, even after multiple preclinical problems with paclitaxel were surmounted, a number of unique clinical problems still required resolution. Despite the existence of over 50 active antineoplastic agents, drug resistance and patient tolerance limit the number of effective agents in specific tumor types. Paclitaxel has shown antitumor activity in multiple clinical trials in cancers of the ovary, breast, head and neck, lung, and gastrointestinal tract. In many of these trials, paclitaxel was active despite evidence of the tumors' resistance to other important drugs. Paclitaxel may be the first of a series or family of drugs: in preliminary trials, an analogue, docetaxel, has also shown significant antineoplastic activity. However, many issues regarding the optimal use of both of these drugs remain unresolved.

Overview: Paclitaxel and Chemotherapy

Schiff and Horowitz's description of paclitaxel's unique mechanism of action was the catalyst for paclitaxel's clinical development *(1)*. The difficulties in translating paclitaxel from the forest to the pharmacy were described in chapters 1 and 2. Additional difficulties awaited clinicians who began using paclitaxel in clinical trials. This chapter will address those clinical problems and the results of therapeutic trials in patients with tumors of the ovaries, breast, head and neck, lungs, or gastrointestinal tract. The trials in ovarian and breast cancers confirmed that paclitaxel has major clinical activity, leading to its approval by the Food and Drug Administration (FDA) for commercial use. The clinical results of trials of a semisynthetic taxane (taxoid), docetaxel (Taxotere), will be also discussed here.

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Clinical Problems Unique to Paclitaxel. The early clinical trials of paclitaxel faced three specific problems.

Hypersensitivity Reactions. The purpose of the first series of trials of a new drug in humans (phase I trials) is to determine the maximum tolerated dose by treating consecutive cohorts of patients with escalating doses of the drug. The maximum tolerated dose is defined by the occurrence of toxic effects, called dose-limiting toxicity, whose severity or permanence limit further dose escalation. In addition to the expected problems of myelosuppression (low white blood cell counts) and neuropathy encountered in the initial phase I trials of paclitaxel, an acute allergic reaction occurred that was fatal in one patient *(2)*. This reaction was similar to the severe reactions experienced by some patients who receive iodinated intravenous contrast medium for radiographic procedures. The unpredictability of this reaction terminated clinical trials until it was discovered that it was rapid infusion of the diluent, Cremophor EL, that caused the reaction. To prevent this, the National Cancer Institute (NCI) recommended infusing paclitaxel over 24 hours and premedication with corticosteroids and antihistamines *(3)*. These strategies have reduced the incidence of serious hypersensitivity reactions to 1% or less. Since both the premedication regimen and the slow infusion duration were developed simultaneously, it was initially unclear which was more important. Further studies have shown that each is effective independently.

Cardiac Toxic Effects. When clinical trials were resumed, all patients were treated in an intensive care unit with cardiac monitoring. Nearly 30% of patients were observed to have an abnormal but generally benign slowing of the cardiac rhythm (sinus bradycardia) while receiving paclitaxel. In a few cases, however, this rhythm was so slow that a pacemaker was required to continue treatment. A few patients with severe but undiagnosed coronary artery occlusions died of myocardial infarctions (heart attacks) or had life-threatening rhythm abnormalities *(4)*. Cardiac monitoring was required in all clinical trials and extensive data were collected. Analysis of 3400 patients revealed that the incidence of life-threatening events was less than 0.5%. Review of trials conducted before these heart problems were observed and of historical data from other drug development studies revealed that multiple benign rhythm abnormalities are common in patients receiving chemotherapy. It was recommended that patients who had known disease of or took drugs affecting the conduction system be given paclitaxel only with cardiac monitoring.

Drug Supply. After phase I trials have determined an effective and safe dose, most active new drugs are tested simultaneously in several trials in specific tumor types (phase II) and at different research centers, with exploration of different infusion durations and retreatment intervals (administration schedules). The early scarcity of paclitaxel meant that the results of each trial had to be carefully evaluated before planning the subsequent trial, that the numbers of patients treated would be limited, that the duration of treatment would be curtailed, that only limited types of tumors would be tested, and that the time frame for the start of these trials was delayed. To determine the level of activity with narrow confidence levels, the usual numbers of patients treated

in a trial of a drug with such high activity would be 35-50 patients. In the early trials in breast cancer, for example, only 25 patients could be treated. Similarly, in a drug with such a high level of activity, most patients would be given at least six treatments before their tumor was judged unresponsive. In the lung cancer studies, patients whose tumors did not evince a 50% or greater shrinkage in the perpendicular diameters of bidimensionally measurable lesions (i.e., an objective response), were removed from study even though clinical information, such as shortness of breath or pain control, suggested they were having clinical benefit. The initial phase II trials were limited to only three tumor types; renal (kidney), melanoma, and ovarian. Of these, only ovarian cancer is fairly common. Finally, although trials in breast cancer were planned in 1985, sufficient supplies of the drug did not become available until 1990. As noted above, improved extraction methods and formulation of a semisynthetic drug have alleviated the supply problem.

Clinical Problems of Chemotherapy. Inherent limitations in the current practice of clinical oncology make paclitaxel a needed addition to the therapeutic armamentarium.

Drug Resistance. Although there are nearly 50 different antineoplastic drugs in use, only a dozen or fewer are effective in the treatment of each specific tumor type because of intrinsic or primary resistance. The initial and subsequent regimens of chemotherapy allow development of secondary or acquired resistance by selecting cells that survive. Ultimately, by a variety of mechanisms, a multiply drug-resistant tumor evolves, and further chemotherapy induces only toxic effects without tumor kill *(5)*. Tumors are classed by their degree of chemosensitivity. Breast and ovarian cancers are moderately sensitive. However, when the tumor becomes resistant to doxorubicin (breast) or cisplatin (ovarian), few other drugs are effective.

Patient Tolerance. As the tumor grows, the patient becomes increasingly debilitated by the accumulation of secondary effects from the tumor (cachexia, pain) or previous treatments (bone marrow or heart muscle failure from irradiation or prior chemotherapy or both) as well as primary effects, which depend on the site of involvement (shortness of breath, liver failure, bone fractures). Thus, with the exception of those with very indolent tumors, most patients have the physical reserve to endure only a limited number of aggressive chemotherapy regimens.

Ovarian Cancer

Background. Ovarian cancer is the leading cause of death among gynecologic malignancies in the USA, surpassing the mortality from cervical and endometrial cancer combined. Approximately one woman in 70 will develop ovarian cancer. In American women it is the sixth most common cancer and the fourth most common cause of death *(6)*. In 1994, 24,000 cases and 13,600 deaths are attributed to ovarian cancer *(7)*. The peak incidence is in the seventh decade; it is uncommon below 50 years of age *(8)*. The incidence is high in North America and Northern Europe, and low in Japan *(9)*.

The cause of ovarian cancer is unknown, but it is associated with consumption

Only about 5% of cases are hereditary. Childbearing and use of birth control pills reduce the risk of developing ovarian cancer by 30-60%, but use of replacement estrogen has no effect on the incidence *(10)*.

The two most important features of the disease which determine outcome are the extent of the disease (stage) and the aggressiveness of the tumor as determined by microscopic evaluation (histologic grade). Unfortunately, 75-85% of patients are diagnosed with advanced disease which has metastasized from the ovaries in the pelvic cavity to the abdominal cavity, because symptoms are often absent until the disease involves other organs in the abdominal cavity. These patients are rarely cured *(11-14)*, but treatment with chemotherapy may reduce symptoms and prolong life.

Standard therapy consists of cyclophosphamide with either cisplatin or its newer analogue, carboplatin. This causes tumor regression in 60-80% of patients of which 30-50% are complete responses (CR). The median duration of survival is 18 to 24 months, and 5- and 10-year survival for ovarian cancer metastatic to the abdominal cavity and elsewhere is 5-20%, and 0-10%, respectively. Carboplatin has less neurologic, kidney, and auditory toxic effects than cisplatin, causes less nausea and vomiting, and provides a better quality of life than cisplatin. However, it is more expensive and causes more depression of the white blood cell and platelet counts (myelosuppression and thrombocytopenia) *(15)*. Hormonal therapies are transiently effective in 10-20% of patients.

Patients whose tumors previously responded to chemotherapy and who have a treatment-free interval of at least six months are defined as potentially "platinum-" or "platin-sensitive," as 30-50% of these patients will have tumor regression if retreated with either carboplatin or cisplatin *(16,17)*. Patients with tumors that are platin-resistant, defined as worsening disease during treatment, persistent disease after four to six treatments, or recurrent disease within 6 months after completing therapy *(18,19)*, have a median survival of 12 months or less, and no currently available drugs have been shown to prolong these patients' life span. It is in this group of patients that new drug treatments are urgently needed and in whom they are first tested.

Paclitaxel Trials in Ovarian Cancer

The initial clinical trials of paclitaxel in humans treated patients with multiple tumor types that had failed all standard therapies. The intent of these trials was to determine the safest and most effective dose (maximum tolerated dose, MTD) and infusion duration (schedule). Evidence of tumor regression is uncommon in such trials. However, unexpectedly, tumor regression was seen in patients with platin-resistant ovarian cancer *(20)*.

Single-agent trials. These above results were the basis for a series of trials in patients with ovarian cancer designed to evaluate antineoplastic activity (phase II trials) of paclitaxel. A total of 111 patients were treated with doses of 100-250 mg/m^2 infused over 24 hours every three weeks *(21-24)*. Overall, 20-37% of patients had tumor

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