Preliminary Results of Two Dose-Finding Studies of Paclitaxel (Taxol) and Carboplatin in Non-Small Cell Lung and Ovarian Cancers: a European Cancer Centre Effort

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Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), given as a 24-hour infusion, and carboplatin have activity in advanced non-small cell lung cancer (NSCLC) and ovarian cancer. Two dose-finding studies were initiated to identify the optimal doses for the paclitaxel/carboplatin combination when paclitaxel is given in a 3-hour infusion. The fact that the pharmacologic interaction between paclitaxel and cisplatin increases the toxicity of paclitaxel when cisplatin is given before it also prompted an investigation of the influence of drug sequence on toxicity and pharmacokinetics in the NSCLC trial. Thirty-three patients with advanced NSCLC and 11 with advanced ovarian cancer previously untreated by chemotherapy have been enrolled to date. In the NSCLC trial escalating doses of paclitaxel were given in combination with a fixed carboplatin dose of 300 mg/m², while both drugs were escalated in the ovarian cancer study. In both studies paclitaxel was infused over 3 hours and carboplatin over 30 minutes, and cycles were repeated every 4 weeks. The most frequent side effect has been neutropenia, although this did not result in any infectious episodes. Alopecia and mild emesis also have been frequently encountered. Mild skin reactions have been reported in a few patients. Bone pain and myalgia occur more frequently at the highest paclitaxel doses. No difference in toxicity has been observed thus far between the two drug sequences in the NSCLC study. Both studies are still accruing patients as the maximum tolerated doses of paclitaxel in combination with carboplatin have not yet been reached (carboplatin 300 mg/m² with paclitaxel 175 mg/m² in the NSCLC study; carboplatin 400 mg/m² with paclitaxel 150 mg/m² in the ovarian cancer study). An investigation of maximum tolerated doses with granulocyte colony-stimulating factor support is planned thereafter.

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Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) is a new and promising microtubule-inhibiting agent with a mechanism of action different from other microtubule-inhibiting agents, such as the vinca alkaloids. Taxanes, in fact, promote microtubule polymerization and inhibit their depolymerization. Paclitaxel, given in 24-hour infusions, has been shown to have significant activity in ovarian cancer, breast cancer, and non-small cell lung cancer (NSCLC). The response to paclitaxel in advanced ovarian cancer pretreated with platinum-containing chemotherapy has ranged from 21% to 37%. In two studies of paclitaxel given as a 24-hour infusion at 200 and 250 mg/m² to patients with advanced NSCLC, the response rates were 24% and 21%, respectively. The dose-limiting toxicity of paclitaxel is neutropenia, while allergic reactions are now easily prevented with the use of premedication. Neurotoxicity becomes more frequent at doses higher than 250 mg/m² given with hematopoietic growth factor support, and is the dose-limiting toxicity in combination with cisplatin.

Carboplatin is an effective drug in advanced ovarian cancer, with activity similar to cisplatin, which is considered to be the standard for first-line chemotherapy in this disease. The cumulative response rate to carboplatin in untreated NSCLC was 12% in 294 patients. Carboplatin’s dose-limiting toxicity is hematologic, with leukopenia being frequent, but thrombocytopenia being cumulative after several cycles of chemotherapy. Carboplatin has less nonhematologic toxicity than cisplatin, which makes possible its administration on an outpatient basis. In particular, neurotoxicity and nephrotoxicity are not observed with carboplatin at the usual therapeutic doses (350 to 400 mg/m³).

Interestingly, the sequence of administration of paclitaxel in combination with cisplatin influenced toxicity in one dose-finding study; when cisplatin was given before paclitaxel, neutropenia was more severe than when cisplatin followed paclitaxel. This increased toxicity was due to the pharmacologic interaction between the two drugs, leading to a larger area under the concentration-time curve for paclitaxel when administered after cisplatin.
The combination of paclitaxel, given as a 3-hour infusion, and carboplatin is being investigated in two different dose-finding studies in ovarian cancer and NSCLC patients previously untreated with chemotherapy. This schedule will eventually facilitate ambulatory treatment for these tumor types. In addition, the influence of sequence of administration of carboplatin and paclitaxel on toxicity and pharmacokinetics is also being investigated in the NSCLC trial.

These two studies are being performed by the European Cancer Centre, which includes investigators from the Academic Medical Center, The Netherlands Cancer Institute, and the Free University Hospital in Amsterdam. Preliminary results are presented here.

PATIENTS AND METHODS

Non-Small Cell Lung Cancer Study

Patients eligible for this study are aged 18 to 75 years with locally advanced or metastatic NSCLC; no prior chemotherapy; measurable, evaluable, or non-evaluable disease; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate hematologic, renal, hepatic, cardiac, and neurologic functions; life expectancy longer than 12 weeks; no second tumor; no brain metastases; and written informed consent. Paclitaxel is given in 500 mL glucose 5% infused over 3 hours by the use of a constant volume infusion pump device; carboplatin is dissolved in 250 mL glucose 5% solution and infused over 30 minutes. Standard premedication is given before paclitaxel, as described in Table 1.

Increasing doses of paclitaxel are given in combination with a fixed carboplatin dose (300 mg/m²), and cycles are repeated every 4 weeks. Six patients at each dose level are randomized to receive either paclitaxel or carboplatin first followed by the other drug in the first cycle, while the alternate sequence was given in the second and following cycles. Blood is collected for pharmacokinetic analysis of both drugs during the first two cycles.

The objectives of this study are to identify the maximum tolerated dose (MTD) of paclitaxel in combination with 300 mg/m² carboplatin, to investigate the influence of sequence of drug administration on toxicity and pharmacokinetics, and to evaluate the toxicity profile and the antitumor response.

Ovarian Cancer Study

Eligible for this study are patients under 70 years of age with stage III (>3 cm) or IV ovarian cancer previously untreated by chemotherapy or radiotherapy; ECOG performance status ≤2; adequate hematologic, renal, hepatic, cardiac, and neurologic functions; and written informed consent.

Doses of paclitaxel and carboplatin are both increased progressively in this study. Carboplatin is given after paclitaxel, and cycles are repeated every 4 weeks. At least three patients are enrolled at each dose level. The infusion schedules for both drugs are identical to those used in the NSCLC study. Objectives of the study are to identify the MTD of paclitaxel as a 3-hour infusion in combination with carboplatin and to evaluate the toxicity and response of the combination.

In both studies, toxicity and response are evaluated according to World Health Organization criteria. Hematologic toxicity is evaluated via biweekly complete blood cell counts with differentials. Response is evaluated every two cycles. In the ovarian cancer study, laparoscopy and possibly laparotomy are indicated in case of clinical complete response. In both studies, dose modification schemas according to toxicity are provided. Before starting chemotherapy and before each chemotherapy cycle, physical examination, hematologic and biochemistry laboratory tests, and appropriate radiologic investigations to assess tumor extension are performed. After achievement of the MTD, in case of leukopenia being the dose-limiting toxicity, further dose escalation with granulocyte colony-stimulating factor support is planned in both studies.

RESULTS

Non-Small Cell Lung Cancer Study

The initial dose level for paclitaxel was 100 mg/m²; thereafter, dose escalations in increments of 25 mg/m² were performed. The characteristics of the 33 patients enrolled in the study thus far are presented in Table 2. Eighty cycles were given (range, 1 to 7 cycles/patient). At all dose levels at least six patients were entered; at the 125 and 175 mg/m² paclitaxel dose levels, seven and eight patients, respectively, were entered because one and two patients, respectively, failed to receive the planned initial courses.

Leukopenia has been the most frequently encountered side effect; thus far it has been of short

| Table 1. Standard Premedication With the Use of Paclitaxel |
|-----------------|-----------------|-----------------|
| **Agent**      | **Dose**        | **Route**       | **Schedule**   |
| Dexamethasone  | 20 mg           | PO              | 12 and 6 hr before paclitaxel |
| Clemastine     | 2 mg            | IV              | 30 min before paclitaxel     |
| Cimetidine     | 300 mg          | IV              | 30 min before paclitaxel     |

Abbreviations: PO, orally; IV, intravenously.
duration and has not induced infections. Furthermore, there has been no clear increase in leukopenia or neutropenia related to the escalating paclitaxel dose. At 175 mg/m² paclitaxel, grade 3 or 4 neutropenia was seen in six of 10 of the first evaluable patients during the first two courses. Thrombocytopenia was not observed during the first two cycles, but was observed in one patient who received more than five cycles of chemotherapy. By comparing the first with the second cycle of chemotherapy, a tendency toward more pronounced hematologic toxicity was present in the second cycle (Table 3). Among the nonhematologic toxicities, nausea and vomiting were mild (prophylactic antiemetic medication was given with ondansetron or metoclopramide), and hypersensitivity reactions were also considered mild. Emesis and allergic reactions were uncommon and mild. Myalgia and bone pain appeared more frequently and were more severe at the highest paclitaxel dose tested (200 mg/m²). Mild peripheral neurotoxicity was infrequently encountered. Most patients who received more than two courses developed some degree of alopecia.

Two early deaths occurred at the 200 mg/m² paclitaxel dose level. The first patient died 1 week after the first cycle. The patient had an ECOG performance status of 2 and was receiving prednisone and furosemide because of dyspnea. Two days after treatment, he developed severe myalgia and bone pain and nausea and vomiting at home. A week after chemotherapy, he was found dead in bed by his wife. Although no life-threatening signs of toxicity were reported, a toxic death could not be ruled out; an autopsy, however, was not allowed. The other patient, in whom tumor regression was already visible 1 week after the first cycle, died a week later due to bowel perforation following necrotic regression of a small bowel metastasis, as demonstrated at autopsy.

Among 20 evaluable patients thus far, there have been two confirmed partial responses, while a minor response was seen in at least two other patients. A progressive reduction of tumor volume was observed in one patient who achieved a partial response after six cycles of chemotherapy. Pharmacokinetic analysis is as yet not completed. However, to date no significant differences have been found between the two administration sequences.

Ovarian Cancer Study

Eleven patients, all with a good ECOG performance status (0 or 1), have entered the study to date. Their main characteristics are summarized in Table 4. Forty-five cycles of chemotherapy have been given (range, 1 to 7 cycles/patient) (Table 5). Neutropenia also has been the main toxicity observed in this study. However, being of short duration, it has been manageable and has not led to

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**Table 2. Non-Small Cell Lung Cancer Study: Patient Characteristics**

| No. of patients | Sex (male/female) | ECOG performance status | Median age (yr) (range) | Histology          | Squamous | Large cell | Adenocarcinoma | Undifferentiated |
|-----------------|-------------------|-------------------------|-------------------------|--------------------|----------|------------|---------------|----------------|}
| 33              | 10/23             | 0, 1, 2                 | 56 (38-75)             | Squamous           | 6        | 10         | 12            | 5              |

**Table 3. Non-Small Cell Lung Cancer Study: Median Nadir Values (Cycle 1/Cycle 2)**

<table>
<thead>
<tr>
<th>Paclitaxel Dose (mg/m²)</th>
<th>WBC (×10⁹/L)</th>
<th>ANC (×10⁹/L)</th>
<th>Platelets (×10⁹/L)</th>
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<td>100</td>
<td>3.3/3.8</td>
<td>1.3/1.2</td>
<td>220/235</td>
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<tr>
<td>175</td>
<td>3.7/3.1</td>
<td>0.9/0.5</td>
<td>250/216</td>
</tr>
</tbody>
</table>

Abbreviations: WBC, white blood cell count; ANC, absolute neutrophil count.

**Table 4. Ovarian Cancer Study: Patient Characteristics**

| Total entered | 11  |
| Stage         |     |
| III           | 6   |
| IV            | 5   |
| Median age (yr) (range) | 55 (22-65) |
| ECOG performance status |     |
| 0             | 4   |
| 1             | 7   |
infection. Moderate thrombocytopenia was observed after several cycles of therapy in two patients (Table 6). Myalgia, bone pain, and neurotoxicity have been negligible (maximum paclitaxel dose reached so far, 150 mg/m²). Alopecia was seen in most patients after a few cycles. No toxic or early deaths have been observed, and at least two partial responses and two complete responses already have been obtained.

**DISCUSSION**

Paclitaxel is the first of a new family of microtubule-inhibiting agents, the taxanes, which exert a different mechanism of action from the other microtubule-inhibiting agents. Paclitaxel already has shown activity in several solid tumors, such as ovarian cancer, breast cancer, and NSCLC. Its activity in these tumor types warrants its investigation as first-line chemotherapy in combination with active agents.

In the present ongoing dose-finding studies, the optimal dose of paclitaxel in combination with carboplatin is being determined in previously untreated ovarian cancer and NSCLC. In addition, the influence of sequence of drug administration is being investigated in the NSCLC study. The rationale for combining paclitaxel with carboplatin is based on the fact that the toxicity of the two drugs is only partially overlapping. In particular, while neutropenia is the dose-limiting toxicity of paclitaxel, thrombocytopenia is a more frequent side effect of prolonged carboplatin administration. Furthermore, neurotoxicity, which is a consistent side effect with high-dose paclitaxel, is not seen with carboplatin at therapeutic doses. These factors, together with the fact that carboplatin can be given on an outpatient basis, make the combination more appealing than the combination of paclitaxel and cisplatin. Dose escalation of paclitaxel in combination with cisplatin has been limited by neuromuscular toxicity (at doses of 250 mg/m² paclitaxel with 75 mg/m² cisplatin using granulocyte colony-stimulating factor support).

The hematologic toxicity (neutropenia) and neurotoxicity of paclitaxel appear to be dose related. The infusion time also influences hematologic toxicity but not neurotoxicity. The 24-hour paclitaxel infusion is clearly more myelosuppressive than 3-hour infusions. The dose of paclitaxel also appears to have some influence on the response rate in ovarian cancer and breast cancer. The difference in activity between infusion times is not significant. In view of its similar activity and lesser myelotoxicity, together with its feasible administration on an outpatient basis, the 3-hour infusion of paclitaxel is certainly a more appealing schedule than the 24-hour infusion schedule.

In the present studies of paclitaxel in combination with carboplatin, the MTDs have not been reached in either study yet (carboplatin 300 mg/m² with paclitaxel 175 mg/m² in the NSCLC study; carboplatin 400 mg/m² with paclitaxel 150 mg/m² in the ovarian cancer study). Providing that leukopenia would be the dose-limiting toxicity in these studies, determination of the MTD will be performed using granulocyte colony-stimulating factor support thereafter. So far the combination has been manageable, with short-lasting episodes of neutropenia. The nonhematologic toxicity has
been mild to moderate, with only muscular pain appearing more pronounced at the highest paclitaxel dose tested in the NSCLC study (200 mg/m²). In both studies there have been clear signs of activity, although it is still too early to define the response rate. Since these are dose-finding studies, response rates should be evaluated preferentially in patients treated at the highest doses tested, as a dose-response relationship was observed in breast and ovarian cancer studies. Of interest is that late-appearing responses have been observed in the NSCLC study, which confirms observations in studies of paclitaxel in ovarian cancer and breast cancer. One patient in the NSCLC study died of unknown causes, and toxicity could not be ruled out as a possible cause of death. This event stresses the fact that administration of combination chemotherapy including paclitaxel at this stage should still be limited to controlled clinical trials.

REFERENCES