lung adenocarcinoma cell line (A_{549} DDP) by continuously exposing cells to gradually increasing doses of DDP for a duration of 8 months. The resistant phenotype of the A_{549} DDP cell line was stable for more than 5 months in the absence of drug. The A_{549} DDP cell line is 24.4-fold resistant to DDP than it's parent cell line (A_{549}) as tested at IC_{50} with MTT assay. Cellular glutathione (GSH) content increased significantly in the A_{549} DDP cell line ($P < 0.01$). D,L-buthionine-S R-sulphoximine (BSO) was used to analyse the role of GSH in the mechanism of resistance to DDP. Pretreatment with BSO (50 m, 48 h, GSH exhausted and not being detectable) increased the DDP-induced cytotoxicity 5-fold in A_{549} DDP but no similar change was noted in A_{549}. Measuring glutathione-S-transferase Ò (GSH-Ò) content by cell ELISA we found that it was approximately 1.6-fold higher in the resistant cell with no evidence of GST gene amplificantion. The A_{549} DDP cell line was remarkably cross-resistant to carboplatin and MTX, but not to ADM, VP-16, and VM-26, etc. The results failed to show evidence of mdrl, Topo II gene amplification nor P-glycoprotein overexpression. It is suggested that the GSH/GST detoxifying systems may play an important role in the resistant phenotype of A_{549} DDP and that the mechanisms of DDP-resistance were not related with mdr in A_{549} DDP cell line.

Etoposide administered orally in the treatment of lung cancer

Zatloukal P, Mericka O, Petruzelka L. *Katerinska 19, 120 00 Praha 2.* Stud Pneumol Phtiseol 1995;55:207-13.

Etoposide is a phase specific cytostatic drug currently used parenterally in the treatment of bronchogenic carcinoma. It has an expressive dependence on dosage schedule. Recently, oral administration is more frequently used in longer dosage schedules. Authors present a review of more important studies dealing with the efficiency of this therapy. Orally administered etoposide given in monotherapy is an effective alternative to combined treatment of small-cell lung carcinoma in cases when combined therapy is risky or for other reasons cannot be applied. The use of oral etoposide in non-small cell lung carcinoma, or replacement, parenteral form to oral administration in combined therapy is currently studied.

Management (chemotherapy/best supportive care) of advanced-stage non- small cell lung cancer

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Non-small cell lung cancer (NSCLC) represents almost three quarters of all cases of lung cancer. Most NSCLC patients present with either locally advanced inoperable disease, stage IV metastatic disease, or comorbid medical conditions that make them unsuitable for curative resection. Among NSCLC patients in the United States, overall 5-year survival rates range from 10% to 15%. Systemic chemotherapy has had minimal impact on prolonging survival or improving quality of life. Combination chemotherapy regimens containing cisplatin usually produce the best overall response rates. Combination chemotherapy in one study also has been shown to be more efficacious and less expensive than best supportive care. Newer cytotoxic agents, including vinorelbine, gemcitabine, paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), docetaxel, and the camptothecins, have shown promise in the treatment of NSCLC. In combination with other effective agents (eg, cisplatin), response rates approaching 50% have been observed. A greater understanding of the biologic properties of lung cancer may help facilitate early detection and chemoprevention in patients at risk.

Paclitaxel 3-hour infusion given alone and combined with carboplatin: Preliminary results of dose-escalation trials

Muggia FH, Vafai D, Natale R, Israel V, Zaretsky S, McRae A et al. *Norris Cancer Center, University of Southern California, 1441 Eastlake Ave, Los Angeles, CA 90033.* Semin Oncol 1995;22:Suppl 9:63-6.

Paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) by 3-hour infusion was combined with carboplatin in a phase I/II study directed to patients with non-small cell lung cancer. Carboplatin was given at a fixed target area under the concentration-time curve of 6.0 by the Calvert formula, whereas paclitaxel was escalated in patient cohorts from 150 mg/m² (dose level I) to 175, 200, 225, and 250 mg/m². The 225 mg/m² level was expanded for the phase II study since the highest level achieved (250 mg/m²) required modification because of nonhematologic toxicities (arthralgia and sensory neuropathy). Therapeutic effects were noted at all dose levels, with objective responses in 17 (two complete and 15 partial regressions) of 41 previously untreated patients. Toxicities were compared with a cohort of patients in a phase I trial of paclitaxel alone at identical dose levels. Carboplatin did not appear to add to the hematologic toxicities observed, and the paclitaxel/carboplatin combination could be dosed every 3 weeks.

Four-day paclitaxel infusion with cisplatin for patients with lung cancer

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Lung cancer cell lines are between seven and 1,000 times more sensitive to paclitaxel (Taxol; Bristol-Myers Squibb Co, Princeton, NJ) when exposed for 120 hours (5 days) compared with 3-hour exposure. A phase I study of 4-day infusion of paclitaxel plus bolus cisplatin for patients with lung cancer has defined the recommended phase II dose. In this study, paclitaxel infused at 30 mg/m²/d for 4 days followed by a cisplatin bolus of 80 mg/m² after infusion completion was associated with acceptable hematologic toxicity. Nine of the 16 patients with non-small cell lung cancer treated with at least two cycles of this regimen attained an objective tumor response (one complete response and eight partial responses; overall response rate, 56%). The recommended phase II dose of a 4-day infusion of paclitaxel plus bolus cisplatin followed by the administration of granulocyte colony-stimulating factor has not yet been determined.

A phase I study of ifosfamide/carboplatin/etoposide/paclitaxel in advanced lung cancer

Strauss GM, Lynch TJ, Elias AD, Jacobs C, Kwiatkowski DJ, Shulman LN et al. *Division of Medical Oncology, Dana-Farber Cancer Institute, 44 Binney St, Boston, MA 02115.* Semin Oncol 1995;22:Suppl 9:70-4.

A phase I study was conducted to define the maximally tolerated dose and toxicity profile of the ifosfamide/carboplatin/etoposide/paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) (ICE-T) regimen in advanced lung cancer. This chemotherapy program uses paclitaxel given as a 24-hour continuous infusion in conjunction with full-dose ICE chemotherapy with growth factor support. The dosage of paclitaxel was escalated from 75 to 225 mg/m². Thirty-four patients have been accrued to date onto this study. Because hematologic dose-limiting toxicity was defined in terms of neutropenia and/or thrombocytopenia exceeding 7 days' duration, no patient demonstrated what was defined by the protocol as dose-limiting toxicity. Nonetheless, substantial hematologic toxicity was observed. Overall, 26% had fever and neutropenia, 56% had grade 4 neutropenia, and 26% had grade 4 thrombocytopenia. In all cases, hematologic toxicity was short term and reversible. While grade 3 and 4 myelosuppression was frequently observed, it was not dose related (in terms of paclitaxel dosage). Nonhematologic toxicity also was not dose related and, with only a few exceptions, was not clinically significant. Among 27 patients evaluable for response, 41% achieved an objective response, including 15% with a complete response. All of five patients with small cell lung cancer responded (including two with a complete response). Among 22 patients with non-small cell lung cancer,

27% achieved an objective response (also including two with a complete response). The results of this study suggest that with growth factor support, it is possible to safely administer full-dose, single-agent paclitaxel in conjunction with full-dose ICE chemotherapy. We will soon be initiating a phase II study of the ICE-T regimen using paclitaxel at 225 mg/m² as a 24-hour continuous infusion in advanced lung cancer. We will also conduct a phase I study of ICE-T, with paclitaxel administered as a 3-hour continuous infusion.

Paclitaxel by 1-hour infusion in combination chemotherapy of stage III non-small cell lung cancer

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We report our preliminary phase II experience with paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) given as a 1-hour infusion with cisplatin, etoposide, and concurrent radiotherapy to patients with unresectable stage IIIA or IIIB non-small cell lung cancer. Twenty-three patients have been started on therapy, with 15 thus far completing treatment. Eight of 15 patients have achieved complete or 'near complete' responses, and five more patients have had partial responses. No patients experienced disease progression. The combined-modality regimen was well tolerated, with the exception of grade 3 or 4 esophagitis, which usually occurred during the last 2 weeks of radiation therapy (eight patients). It is hoped the results of these and other studies will help clarify the role of paclitaxel in multimodality therapy for lung cancer.

Dose-finding and sequencing study of paclitaxel and carboplatin in non-small cell lung cancer

Giaccone G, Huizing H, Postmus PE, Huinink WWTB, Koolen M, Van Zandwijk N. et al. *Department of Oncology, Free University Hospital, De Boelelaan 1117, HV 1081 Amsterdam.* Semin Oncol 1995;22:Suppl 9:78-82.

A dose-finding study was set up to identify the optimal dose of the combination of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ) and carboplatin for phase II studies in patients with advanced chemotherapy-naive non-small cell lung cancer (NSCLC). The influence of drug sequence on the toxicity and pharmacokinetics of both agents was also assessed. To develop an ambulatory regimen for palliation of advanced NSCLC, paclitaxel was infused over 3 hours with standard premedication and carboplatin over 30 minutes. Cycles were repeated every 4 weeks. At each dose level, at least six patients were randomized to receive either paclitaxel followed by carboplatin or the reverse sequence. In the second and following cycles the alternate sequence was administered. The pharmacokinetics of both paclitaxel and carboplatin were compared in the first two cycles in at least two patients per dose level. Sixty-two patients have been entered in this study. Paclitaxel was increased from 100 mg/m² in 25 mg/m² increments up to a maximum of 225 mg/m² combined with a fixed carboplatin dose (300 mg/m²). Thereafter, the drug doses were increased to a maximum of 400 mg/m² carboplatin and 250 mg/m² paclitaxel. In 243 cycles, the most frequent side effects were neutropenia, alopecia, and mild emesis. Only one patient developed a major hypersensitivity reaction to paclitaxel. Bone pain, myalgia, and peripheral neurotoxicity occurred more frequently at paclitaxel doses above 200 mg/m². No significant differences in toxicity or in the pharmacokinetics of either drug were observed between the two drug sequences. The pharmacokinetics of paclitaxel were nonlinear and consistent with saturation. At the highest paclitaxel dose (250 mg/m² with carboplatin 350 mg/m²) a toxic death due to severe leukopenia, thrombocytopenia, and hemorrhage occurred. Safe doses for phase II trials in untreated NSCLC are 200 mg/m² paclitaxel with 300 mg/m² carboplatin. Of 50 evaluable patients, five of the six major responses were observed at paclitaxel doses of 175 mg/m² and above, which suggests a dose-response relationship for paclitaxel in NSCLC.

Phase I study of paclitaxel as a 3-hour infusion followed by carboplatin in untreated patients with stage IV non-small cell lung cancer

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Preliminary results of a phase I study of paclitaxel (Taxol; Bristol-Myers Squibb Company, Princeton, NJ), given by 3-hour infusion, followed by carboplatin in chemotherapy-naive patients with stage IV non-small cell lung cancer indicate that both agents can be combined at clinically relevant single-agent doses. The paclitaxel (mg/m²)/carboplatin area under the concentration-time curve (mg · min/mL) dose level of 225/7 is projected to be the maximally tolerated and recommended phase II dose level for future evaluations. Dose-limiting neutropenia, thrombocytopenia, and nausea and vomiting preclude treatment with carboplatin doses estimated to target an area under the concentration-time curve of 9 mg · min/mL when given with paclitaxel 225 mg/m². The heterogeneous nature of the principal toxicities, as well as the ability to administer clinically relevant single-agent doses of both agents in combination, also indicate that further dose escalation of paclitaxel and carboplatin using hematopoietic growth factors would not be feasible. The preliminary antitumor activity noted to date, as well as the safety associated with the clinically relevant single-agent doses that can be given in combination, indicate that phase II/III evaluations of this regimen are warranted in patients with both advanced and early stage non-small cell lung cancer.

Paclitaxel and ifosfamide: A multicenter phase I study in advanced non-small cell lung cancer

Hoffman PC, Krauss SA, Drinkard LC, Masters GA, Samuels BL, Bitran JD et al. *Section of Hematology/Oncology, University of Chicago, MC2115, 5841 S Maryland Ave, Chicago, IL 60637.* Semin Oncol 1995;22:Suppl 9:38-41.

Both paclitaxel and ifosfamide have significant single-agent activity in non-small cell lung cancer. We designed a phase I study combining escalating doses of paclitaxel, administered by 24-hour infusion, with ifosfamide given at a dose of 1.6 g/m² daily x 3. Paclitaxel dose levels were 135, 170, 200, 250, and 300 mg/m². The goal of the study was to determine the maximum tolerated dose and dose-limiting toxicities of paclitaxel when used in this combination. Dose escalation was possible because of the use of filgrastim, a granulocyte colony-stimulating factor. Twenty-five patients at three institutions were treated. The dose-limiting toxicity of the combination was granulocytopenia, with other toxicities being generally mild to moderate. The maximum tolerated dose of paclitaxel was 300 mg/m², and the recommended phase II dose is 250 mg/m². There was a suggestion of a dose-response curve with paclitaxel as all three partial responses were seen at the 250 mg/m² dose level. An additional II patients had objective regression or stable disease lasting for 9 to 30 weeks. A phase II study of this combination is currently being planned by the Cancer and Leukemia Group B.

Paclitaxel plus carboplatin for advanced lung cancer: Preliminary results of a Vanderbilt University Phase II Trial - LUN-46

Johnson DH, Paul DM, Hande KR, DeVore RF III. *Division of Medical Oncology, 1956 The Vanderbilt Clinic, Nashville, TN 37232-5536.* Semin Oncol 1995;22: Suppl 9:30-3.