The first attempts of LL (immune) *in vitro* stimulation between the ALCT courses by means of native IL-2 with the dose 100 IE per 1 ml of the auto-lymph: as it was found, there was more than 50% increase in LL-activity, as well as in improvement in the course of the treatment.

1102 PUBLICATION

**LACK OF PROGNOSTIC SIGNIFICANCE OF IMMUNOHISTOCHEMICAL DETECTION OF P53 IN NON-SMALL CELL LUNG CANCER (NSCLC)**

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The aim of this study was to establish whether immunohistochemical detected expression of p53 protein is related to prognosis in NSCLC. From 1984 to 1991 tissue samples were obtained from 186 surgical treated patients with NSCLC (squamous cell = SQ 104; adenocarcinoma = AD 59; large cell carcinoma = LA 22). The protein-product of the tumor suppressor gene p53 was analyzed on cryostat sections using the peroxidase Labelled Strept-Avidin-Biotin technique. P53 protein was visualized by the monoclonal antibody DO7 (DAKO), the percentage of tumor cells with nuclear staining (grade 0, grade 1 = 1–29%, grade 2 = 30–59%, grade 3 = 60–100%) was estimated and results were correlated with clinical characteristics. Grade 3 expression was found in 45% of tumors. p53 expression was neither correlated to tumor size, nodal status, stage or survival.

p53 may be important in the carcinogenesis of lung cancer but of little significance in established tumors.

1103 PUBLICATION

**LUNG CANCER AT DIAGNOSIS AND RESPIRATORY INFECTIONS**

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The prevalence of pulmonary infections in lung cancer at diagnosis was investigated in 96 patients submitted to bronchoscopy showing endobronchial tumor. Bronchoalveolar lavage (BAL) was carried-out instilling 60 ml of steril normal saline; The fluid recovered was immediately cultured for quantitative microbiological analysis. 42 micro-organisms (m.o.) were cultured from the BAL fluids of 33 patients (34.3%). 50% were Gram– 33% Gram+, 17 other m.o. Haemophilus species were the most frequent Gram– Staphilo coccus Aureus the most frequent Gram+. No relationship was found between respiratory infections and stage of the disease, performance status, histologic type, immunoregulatory ratio and serum lymphocyte subsets.

A quantitative BAL culture may be useful in patients with lung cancer at diagnosis, as respiratory infections are frequent and, if unrecognized and untreated, can become a risk factor when immunocompetence is impaired by chemotherapy or advancement in the stage of malignancy.

1104 PUBLICATION

**(LACK OF) CORRELATION BETWEEN CARBOPLATIN (CBDCA) DOSE AND TREATMENT OUTCOME IN SQUAMOUS CELL BRONCHOGENIC CARCINOMA (NSCLC)**

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In a prospective study 160 untreated patients with clinical stage IIIb and IV NSCLC were randomized to receive vindesin-mitomycin C-cisplatin or vindesin-mitomycin C—CBDCA (at fixed dose of 500 mgsqm). The drug free interval was 4 wks and patients were supposed to receive 6–8 cycles. CBDCA group obtained an response rate of 38% with median survival 6.2 mo. and experienced relatively mild toxicity. Received dose intensity (DI) for CBDCA was calculated to be 91% of planned DI. The treatment outcome was analyzed by the influence of CBDCA DI in respect of optimal individual dose calculated by Egorin, Calvert and Chatelut (ESMO Lisbon) formulas. Coefficients of variation between the dose of CBDCA based on body surface area and individual dose obtained by Calvert and Egorin formula were 30 and 40% respectively. Patients with PD received approximately 15% less of optimal dose compared to the patients with CR only, but small numbers of CRs do not allow firm conclusion. Due to broad range of pretreatment platelet count, Calvert formula might not be suitable for optimal dose finding in NSCLC patients. It is concluded that DI-outcome correlations are not consistent for CBDCA in NSCLC. It is of questionable value to test this hypothesis in a prospective manner due to lack of sensitivity of NSCLC to chemotherapy agents available.

1105 PUBLICATION

**A SURVEY ON CLINICAL PRACTICE WITH HYPERFRACTIONATED RADIOTHERAPY (HFX) AND CONCOMITANT CISPLATIN IN STAGE III NON SMALL CELL LUNG CANCER**

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To define the toxicity and effectiveness of concomitant Chemotherapy (CTH) and HFX in Non Small Cell Lung Cancer (NSCLC), a phase I/II study was conducted with Cisplatin 4 mg/day (16 mg/mq/week) given during two daily fractions irradiation (1.2 Gy, 6 hours apart) to 69.6 Gy in 58 fractions in a 6 weeks time. Thirty-six eligible patients (PTS) (81% males, 58% squamous, 25% adeno, 17% NSC—carcinomas, 53% stage III B) were treated in 5 different lospitals. Protocol treatment was completed in 56% of the PTS; in 81% the total radiation was > 66 Gy; in 69% Cisplatino total dose was >64 mg/mq. Acute toxicity was (EORTC scale): 17% esophagitis grade (gr) 3, 31% gr 2—upper GI 3% gr 3, 11% gr 2—hematologic 11% gr 2–3. There was a subacute lung toxicity death. Median survival time was 14 months (range 6–21); 25 PTS (69%) died, 4 (11%) are alive with disease and 7 (19%) alive and well. Concurrent CHT and HPX for NSCLC appears to be feasible, but short-term seem not to be better than in standard treatments.

1106 PUBLICATION

**AMIFOSTINE (A), CISPLATIN (C), VINBLASTINE (V): A HIGHLY ACTIVE REGIMEN FOR NON SMALL CELL LUNG CANCER (NSCLC)**

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Monthly cycles of A, 740–910 mg/m$^2$, C, 120 mg/m$^2$ were given on Day 1 & V, 5 mg/m$^2$ weekly to 24 Stage IIIA/B & 23 stage IV NSCLC pts. After 2 cycles ACV, Stage III pts received 60 Gy chest RT. 67% stage III, 65% Stage IV responded to ACV. Median follow-ups for Stage III and IV pts are 31 & 15 mos; 1 year survivals are 53% & 60%, respectively. Median survival for Stage III is 16 mos and for Stage IV is estimated to be 17 mos. The spectrum of toxicities from ACV were similar in Stage III/IV pts. A was given on day 1 to protect from C toxicities. Though transient increases in serum creatinine $\geqslant$2 mg/m$^2$ were noted, protracted elevations lasting beyond day 28 occurred in only 6% (3/47). 11 stage IV pts received $\geqslant$4 cycles therapy. None sustained $\geqslant$40% reduction from baseline creatinine clearance (CrCl). This is in contrast to other trials using $\geqslant$4 cycles of 100 mg/m$^2$ C in which 30–45% of the pts sustained $\geqslant$40% decrease in CrCl. Grade 4 neutropenia primarily related to weekly V given without A occurred in 46% of cycles. Toxicities from A were nausea/vomiting & transient hypotension. We conclude that amifostine appears to improve the therapeutic index of CV in NSCLC as evidenced by both high response rates & reduced cumulative renal toxicity. This is being tested in a multicenter randomized trial.

1107 PUBLICATION

**PACLITAXEL SINGLE AGENT IN THE FIRST-LINE TREATMENT OF ADVANCED NSCLC**

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Taxol has produced the best response rate (21%) to date of all single agents in ECOG trials in NSCLC, with is activity confirmed at M.D. Anderson. In 1/94, we initiated a phase II trial of taxol single agent in patients with stage IIIb/IV NSCLC and no prior radio- and/or chemotherapy. In this trial, paclitaxel was administered over 3 h at a dose of 200 mg/m$^2$ after premedication with dexamthasone, cimetidine and clemastine. The second and all further cycles were administered in an outpatient setting. Cycles were repeated at 28-day intervals. In this ongoing study, 25 patients—21 men and 4 women—with a median age of 60.4 (range, 42 to 69) have been treated to date. Patient characteristics included ECOG performance status 0–1, stage IIIb 7 and stage IV 18; and a histological diagnosis of squamous cell carcinoma in 15 patients (60%), adenocarcinoma 8 patients (32%), and 2 patients (8%) with poorly differentiated carcinoma. At this time, partial remissions have been noted

in 7 patients (28%), no change occurred in 9 patients (36%) and 9 patients (36%) had progressive disease. Hematologic toxicities were mild; only one grade 3/4 (WHO) neutropenia was observed. Grade 3/4 myalgia was observed in 3 patients, and grade 4 constipation in one patient, further appeared in 9 men impotence.

Conclusion, these results indicate that paclitaxel is an active new agent for the treatment of advanced NSCLC. Mild hematologic and nonhematologic toxicity's were observed with the 3-h Infusion. The firstly described appearance of impotence needs to be clarified in further investigations. The therapy was generally well tolerated.

1108 PUBLICATION

## COMBINATION CHEMOTHERAPY INCLUDING IFOSFAMIDE, CARBOPLATIN, AND CISPLATIN IN ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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There is currently no standard chemotherapy regimen for treatment of non-resectable NSCLC. We evaluated a combination of Ifosfamide (IFX; 1500 mg/m$^2$ i.v. day 1–3), Carboplatin (CBDCA; 200 mg/m$^2$ i.v. day 1), and Cisplatin (CDDP; 50 mg/m$^2$ i.v. day 2–3), together with mesnuroprotection and hydration, every 4 weeks. Patients (pts) had histologically verified, previously untreated, measurable or evaluable non-resectable NSCLC, without brain metastases and with normal organ functions. 28 pts are currently included with the following characteristics: median age 48 years (range 38–67), WHO performance status (0: 32%, 1: 61%, 2: 7%), stage (Ia: 7%, IIIb: 46%, IV: 46%), histology (squamous cell 21%, adenocarcinoma 42%, large cell carcinoma 21%, poorly differentiated NSCLC 14%). *Results:* Median no. of treatment courses were 3 (range 1–8). WHO grade 3–4 leucopenia occurred in 37% of pts and thrombocytopenia in 61% of pts. There were 2 cases with neutropenic fewer (duration 2 and 3 days), and 6 cases with WHO grade 1–2 bleeding. There were no toxic deaths. Nausea/vomiting WHO grade 3–4 occurred in 25% in spite of premedication with Granisetrone and Prednisolone. 6 partial and 3 complete responses have been recorded in this ongoing trial (response rate 32%). In conclusion, this regimen of IFX+CBDCA+CDDP is active in advanced NSCLC. The regimen is confined with hematologic toxicity, but the side effects are managable.

1109 PUBLICATION

## DETECTION OF HUMAN PAPILLOMAVIRUS DNA IN PRIMARY LUNG CARCINOMA BY NESTED POLYMERASE CHAIN REACTION

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Human papillomaviruses (HPV) have been implicated in the pathogenesis of human squamous cell carcinoma, especially of cervical carcinomas. In two previous studies concerning squamous cell carcinomas of the lung, DNA to HPV subtypes 6/11/16/18 (and 31/33/35 for one study) was detected by *in situ* hybridization in 7 to 30% of the cases. A series of 31 frozen biopsies of lung carcinomas were examined for the presence of HPV DNA by nested polymerase chain reaction (PCR). Primers for the two PCR were type-specific primers (6/11–16 and 18; kit Amplicis HPV*) for the transforming region of HPV. HPV DNA is found in two of 18 cases of squamous cell carcinoma (11%), in one of 4 cases of adenocarcinoma, and in two of 7 cases of neuro-endocrin cancers. No case of the two large cell undifferentiated carcinomas was positive. There were three cases of HPV 6/11, one case of HPV 16, and one sample positive for HPV 6/11 and HPV 18. No morphologic changes consistent with HPV lesions were seen, and squamous metaplasia was observed only in squamous cell carcinomas. The frequency of 11% among the squamous cell carcinomas is near those found by previous studies, whereas PCR is theoretically more sensitive than *in situ* hybridization. HPVs have never been detected in adenocarcinomas or neuroendocrin tumors, and this has to be confirmed by studies of many more cases. So HPV might play a role as promoter in carcinogenesis of any types of lung carcinoma, although at a low frequency.

1110 PUBLICATION

## VINDESINE-IFOSFAMIDE-PLATINUM (VIP) CHEMOTHERAPY IN PATIENTS WITH INOPERABLE STAGE III AND IV NON SMALL CELL LUNG CANCER. A PHASE II TRIAL

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Between Sept. 1991 and Oct. 1993, 64 patients were enrolled in this multicenter study in order to evaluate the toxicity and efficacy of a chemotherapy regimen, combining three active compounds while avoiding the pulmonary and other toxicity of mitomycin C.

Vindesine 3 mg/m$^2$ day 1 and 8, Ifosfamide 1200 mg/m$^2$ and Platinum 30 mg/m$^2$ day 1, 2 and 3 were given every 28 days. Response was evaluated each 2 courses, responders were continued until 6 courses.

*Patients characteristics:* mean age 57 y (37–70), histology squamous 19/adeno 16/large cell 8, metastatic disease in 27.

Responses in 59 patients evaluable for response were as follows:

| | total | stage III | stage IV |
|---|---|---|---|
| CR | 3 (5%) | 2 (10%) | 1 (3%) |
| PR | 22 (37%) | 9 (43%) | 13 (34%) |
| SD | 23 (39%) | 6 (28%) | 17 (45%) |
| PD | 11 (19%) | 4 (19%) | 7 (18%) |

WHO grade 3 & 4 toxicity scores were: anemia 6 pts, neutropenia 7 pts (4 gr. 4 infections), thrombopenia 5 pts, nausea 14 pts, alopecia 33 pts, neurotoxicity 3 pts and ototoxicity 1 pt. No > gr. 2 renal toxicity.

*Conclusion:* This VIP regimen is very active in this group of patients with moderate toxicity, and deserves further study as induction chemotherapy.

1111 PUBLICATION

## A PHASE II STUDY OF PACLITAXEL IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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Paclitaxel is a product from the bark of *Taxus brevifolia* (Western Yew) with broad activities in various types of solid tumors. It has been used as second lined chemotherapy for advanced ovarian and breast cancer. We conducted a phase II study of paclitaxel as a single agent chemotherapy in Thai NSCLC patients. The treatment dosage and schedule are 200 mg/m$^2$ infusion over 24 hours every 21 days with dose adjustment according to toxicities. Dexamethasone, chlorpheniramine and cimetidine were given as prophylaxis regimens for allergic reactions and G-CSF was given for prophylaxis of neutropenia. Total patients enrolled in the study were 23. Nineteen patients were evaluated for tumor response and 23 for chemotherapy toxicities. Of all evaluable patients, 16 had no previous chemotherapy, 5 had prior radiotherapy, 5 had previous surgical resections. Median age was 54 (range 35–79). Male to female ratio was 1:1. Pretreatment performance status were 1 in 20 (87.0%) pts, 2 in 2 (8.7%) and 3 in 1 (4.3%). Histological diagnosis included adenocarcinoma 17 (73.9%), squamous cell carcinoma 5 (21.7%) and bronchoalveolar 1 (4.4%) pts. Severe toxicities, grade 3 to 4, were alopecia in 21 pts, neutropenia 11, anemia 3, anorexia 1, nausea/vomiting 2, diarrhea 2, myalgia 5. Febrile neutropenia occurred in 4 cycles of chemotherapy of patients who recovered without serious sequele. Result of treatment were 6 (26.1%) PR, 4 (17.4%) SD, and 13 (56.5%) PD. Median time to response and duration of response were 8 weeks and 16 weeks respectively. Sites of response included soft tissue (1 pt), pulmonary (4 pts), mediastinal lymph node (1 pt), liver (1 pt), and bone (1 pt). Eight died from progressive disease, 4 are continuing treatment with paclitaxel and 11 patients switched to other treatments or best supportive care. Paclitaxel as a single agent chemotherapy is an active agent in advanced NSCLC patients.

1112 PUBLICATION

## THE SURVIVAL BENEFIT OF MAINTENANCE THERAPY OF NSCLC PTS RESPONDING TO INITIAL TREATMENT. A RANDOMISED TRIAL

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NSCLC pts with inoperable disease responding to initial therapy usually fare better than those receiving only supportive care. The aim of this