1066 POSTER

A feasibility study of vinorelbine (VNR) and gemcitabine (GEM) in inoperable stage IIIb–IV NSCLC

K. Mattson[1], K. Tamminen[1], V. Nikkanen[1], M. Viren[1], O.-P. Isokangas[1], F. Le Bras[2], I. Barbet[2]. [1]*The Finnish Lung Cancer Group;* [2]*Pierre Fabre Oncologie, Paris*

Purpose: VNR and GEM have significant activity in NSCLC, both as single agents (RR = 21–30%) and in combination with cisplatin (RR = 30–40%). This Phase I–II trial aims to evaluate the response to concurrent VNR and GEM, as well as response duration, time to progression, survival and toxicity.

Methods: Patients (pts) initially received VNR 30 mg/m^2 weekly on days 1, 8, 15 and 22 of a 28 day cycle, and GEM at 1000 mg/m^2 on days 1, 8 and 15. Initial treatment consisted of 3 cycles with pts achieving NC/PR/CR being given a further 3 courses, and those with PR/CR after 6 courses continuing the treatment until relapse. Entry criteria include histologically or cytologically confirmed Stage IIIb or IV NSCLC, no previous chemotherapy or radiotherapy, PS $\leq$ 2, and informed consent.

Results: Haematological toxicity (neutropenia) has necessitated reductions or delays in the administration of VNR and/or GEM in the first 7 patients. Overall dose intensity has been reduced to 70%. We have therefore modified the schedule to VNR 30–35 mg/m^2 and GEM 1000–1200 mg/m^2 on days 1 and 15 of each 28 day cycle. This fortnightly schedule allows the full protocol dose to be administered as well as being very convenient and cost-effective. The first two cycles of the new schedule have only caused minor toxicities. Two responses have been recorded in the 7 patients who have received $\geq$3 cycles of VNR and GEM. The completed Phase I–II results will be presented.

1067 POSTER

p53 mutations in lung cancers of former german uranium miners

W. Popp[1], C. Vahrenholz[1], P. Bauer[2], B. Wiesner[3], F. Täuscher[4], K. Morgenroth[5], N. Konietzko[2], H. Schuster[4], U. Werfel[1], K. Norpoth[1]. [1]*Institute of Hygiene and Occupational Medicine, University of Essen;* [2]*Ruhrland Clinics, Essen;* [3]*Central Clinics, Bad Berka;* [4]*Surgical clinics, Clinical Center of Gera;* [5]*Institute of Pathology, University of Bochum, Germany*

Purpose: Taylor (Lancet 343, 1994, 86) reported about hot spot mutations at codon 249 of the p53 gene in lung cancers of former uranium miners in the USA. We started an investigation in order to get more knowledge about similar mutations in former German uranium miners.

Methods: Until now we investigated 21 former German uranium miners with lung cancers (17 squamous cell cancers). Tumor tissue was investigated by PCR and sequencing for p53 mutations (exons 5–8).

Results: We found no mutation at codon 249 of p53. There were mutations and one deletion in the tumor tissues of 4 patients: codon 154/2: G→T; codon 213/3: A→G; codon 266/1: G→A; codon 272: deletion of 4 bases. Three of the patients were smokers, the G→T transversion was in a nonsmoker.

Conclusions: Our results do not confirm a hot spot mutation in exon 7 of p53 in lung cancers of former German uranium miners. The study is still ongoing.

1068 POSTER

First line treatment of advanced non-small cell lung cancer with doxetaxel and cis-platin: A multicenter phase II study

N. Androulakis, C. Kourousis, S. Kakolyris, A.M. Dimopoulos, E. Papadakis, F. Apostolopoulou, J. Vlachonicolis, D. Hatzidaki, G. Samonis, V. Georgoulias. *Depts. of Medical Oncoloy, Univ. General Hospital of Heraklion, Crete, Dept. of Clinical Therapeutics, Univ. of Athens, First Dept. of Respiratory Diseases, Sotiria Hospital of Athens, Third Dept. of Respiratory Diseases, Sismanoglion Hospital of Athens, Greece*

Purpose: To evaluate the efficacy ans safety of a docetaxel-cisplatin combination in patients with advanced non-small-cell lung cancer (NSCLC).

Methods: Eligibility criteria included chemotherapy-naive patients, with histologically confirmed, measurable, stage IIIB or IV NSCLC, a WHO performance status between 0 and 2, adequate hematologic parameters, and adequate renal, hepatic and cardiac function. Patients received docetaxel (100 mg/m^2) over 1-hour infusion on day 1 and cisplatin (80 mg/m^2) over 30-min infusion with appropriate hydration on day 2. Granulocyte colony-stimulating factor (G-CSF: 150 μg/m^2, SC) was given on days 5–15. Treatment was repeated every 21 days for a maximum of 9 courses or until disease progression.

Results: Fifty three patients were enrolled (28 with stage IIIB and 25 with stage IV disease); all were assessable for toxicity and 50 for response. Grade 3/4 granulocytopenia occurred in 23 patients, 15 of whom were hospitalized for neutropenic fever and 2 died from sepsis. Grade 2 neurotoxicity was observed in 6 patients and grade 3 in 5 patients; grade 3 fatigue occurred in 7 patients, grade 3/4 mucositis in 4 patients and grade 3/4 diarrhea in 6 patients. Mild allergic reactions were observed in 5 patients and mild edema in 4 patients. One complete and 23 partial responses were obsserved (ORR· 48%: 95% C.I.: 34.1–61.8%). The median time to progression was 36 weeks and the median survival time was 56 weeks: the probability for 1-year survival was 58%. The median dose intensity was 30 mg/m^2/week for docetaxel and 24 mg/m^2/week for cisplatin, corresponding to 91% and 89% of the protocol planned doses, respectively.

Conclusion: The docetaxel-cisplatin combonation is an active regimen in advanced NSCLC, with leucopenia being the main toxicity, despite the prophylactic use of G-CSF.

1069 POSTER

An overview of 3 phase II trials of navelbine (NVB), and fractionated doses of cisplatin (CDDP) in the management of advanced non-small cell lung cancer (NSCLC)

M. Pawlicki[2], J. Rodrigues[1], D. Firat[3], J. Altino[1], K. Krawczyk[2], Barista, F. Le Bras[4], J.P. Burillon[4], F.M. Delgado[4]. [1]*ELAN do, Brazil;* [2]*Ankara University, Turkey;* [4]*Institut de Recherche Pierre Fabre, France;* [3]*Oncol. Centre, Krakow and Inst for Tuberculosis & Lung Disease, Warsaw, Poland*

Aim: The combination of NVB and CDDP has shown statistically superior survival compared with standard therapy (JCO 1994, ASCO 1996). 3 phase II studies were conducted to assess a new schedule of this combination which can be given on an out-patient basis: NVB 25 mg/m^2 (1 trial 30 mg/m^2) on day 1 & 5 and CDDP 20 mg/m^2 daily over 5 days (D1–5) every 21 days, (maximum 6 cycles). **Results:** Between 7/94 and 2/96, 127 (pts) were included: median age 60 (34–75). 112 (88%) males; PS 0, 1 and 2, 16%, 55% and 27% respectively. squamous cell – 56%, adenocarcinoma – 36% and large cell – 8%; 12% stage IIIA, 36% stage IIIB and 49% stage IV and 3% unknown (metastatic). 471 courses were administered (median 4, range 1–8). WHO grade (G) 3–4 neutropenia – 12%; G3–4 infection episodes 1.4% of courses. G3 nausea/vomiting: 18% (5.4% of courses). Only 4% of pts developed WHO grade 3 constipation and grade 3–4 peripheral neuropathy was observed in 9% of pts (2.4% G 4). G3 alopecia – 12%. The **overall response rates** observed in Brazilian, Polish and Turkish studies are 46%, 47% (N 30 mg/m^2) and 29% respectively; median TTP: 7.4 months and median survival is: 9.2 months **Conclusion:** These results confirm that NVB + CDDP in combination have constant and reproducible high antitumour activity in NSCLC. This new schedule seems well suited for use in the out patient management of NSCLC.

1070 PUBLICATION

Dose scheduling & drug tolerability in phase II studies of gemcitabine and cisplatin chemotherapy for non-small cell lung cancer

RP. Abratt[1], A. Sandler[2], L. Crino[3], W. Steward[4], F. Shepherd[5], MR. Green[6], B. Nguyen[7]. [1]*University of Cape Town, S Africa;* [2]*Indianapolis;* [6]*Charleston;* [7]*Eli Lilly, Indianapolis, USA;* [3]*Perugia, Italy;* [4]*Leicester, UK;* [5]*Toronto, Canada*

Purpose: To evaluate the influence of scheduling on drug tolerability.

Methods: In 5 phase II studies in NSCLC, gemcitabine was given at 1000 mg/m^2 on days 1, 8 and 15 and cisplatin was given as shown in the Table at 100 mg/m^2 or 30 mg/m^2 (1 study).

Cisplatin given	d1	d2	d15	d15	d1, 8, 15
Med gem dose mg/m^2	718	824	872	957	800
Med cis dose mg/m^2	98	100	94	98	28 × 3
Patients entering cycle (% receiving full dose of gemcitabine)					
Cycle 1	30 (27)	48 (54)	53 (79)	60 (93)	NA
Cycle 2	23 (35)	43 (44)	42 (71)	52 (83)	NA
Cycle 3	18 (22)	37 (38)	35 (77)	45 (64)	NA
Granulocytopenia G4%	13	9	19	20	24
Thrombocytopenia G4%	20	27	8	7	12
Response rate %	33	54	52	38	30
Median survival (mo).	8.4	15 4	13	10.2	8.4
1 yr survival prob %	37	59	55	40	30

Results: The median number of cycles given was 3 to 4.

In both the day 1 & day 2 cisplatin studies, there was a high rate of omission (34% and 52%) of infusions of gemcitabine on day 15 because of thrombocytopenia. This was less than 20% in the day 15 cisplatin studies.

Conclusion: No conclusion can be made on relative survival and response rates as this depends on patient selection. The day 15 regimens are associated with the best tolerability.

Drug exposure duration is important to the activity of phase specific agents (eg gemcitabine).

1071 PUBLICATION

Conservative endbronchial treatment of non-small cell lung cancer

S. Cicėnas[1], A. Jackevičius[2], E. Aleknavičius[3], B. Aleknavičienė[4], P. Breivis[5]. [1,2]*Dept. of Thoracic Surgery;* [3,4]*Dept. of Radiology;* [5]*Dept. of Medical Oncology, Lithuanian Cancer Center, Vilnius, Lithuania*

Objectives were: to evaluate intratumoural injected bleomycine (BL) action during radiotherapy with dynamic fractions (RDF), second, to underline the effectiveness of photodynamic therapy (PDT) using heamatoporphyrin and metal vapour laser combining with conventional external beam radiation in patients (pts) with central type locally advanced NSCLC.

Methods: From 1989–1994 48 pts with NSCLC underwent intratumoural BL injections and RDF. The day we injected BL we use 4 Gy of RDF. Summary dosage of BL was 250.0–300.0 and 65 Gy of RDT. These pts were randomised with 46 pts of control group – only conventional RT.

From 1992–1995 16 pts with NSCLC underwent PDT with haematoporphyrin and metal vapour laser. 4 pts underwent this treatment with local reccurences after surgery. 8 pts with partial tumour response receive additionally – 40 Gy of conventional RT and were randomised with 12 pts control group – only RT.

Results: *First group of pts:* **1.** Partial tumour response we achieved in 31 pts (64.5%) with T2N2M0 and 12 pts (25%) with T3N2M0, no response in 5 pts (10.4%) with T3N3M0. **2.** Endobronchial BI injections causes coagulative tumour necrosis. *Second group of pts:* **1.** Full tumour response we advieved in 8 pts (50%), no response – in 4 pts (25%) with reccurens and 4 pts (12.5%) with T3N2M0 **2.** Combining PDT and RT improves rapidly pts PS and prolongs tumour relapse free period.

1072 PUBLICATION

Oral etoposide in patients with small cell lung cancer

E. Topuz, F. Taş, A. Aydiner, C. Demir, P. Saip, T. Salepci, A. Karadeniz, N. Ertürk. *University of Istanbul, Institute of Oncology, Istanbul, Turkey*

Purpose: To investigate the efficacy, tolerability, and survival of oral Etoposide (E) usage and prognostic factors influencing survival in small cell lung cancer (SCLC).

Methods: Between January 1993 to December 1996, histologically newly diagnosed and previously untreated 49 patients (pts) (45 men, 4 women) were included. Pts were with age ≥70 (23 pts) and pts who were unsuitable candidates for standard intravenous (IV) chemotherapy (CT) with age <70 (26 pts). Median age was 70 (43–81) and all pts had ECOG PS ≤ 3. Thirty pts (%61) had limited disease, while 19 pts (%39) had extended disease. It was given E capsules orally 50 mg bid for 10 days every 21 days as outpatiently. After 3 courses, responses were evaluated radiologically. In responded pts therapy continued until either progression or unexceptable toxicity occurred. Response and toxicity were evaluated according to WHO criterias.

Results: Eleven (%22) pts had partial responses, 17 (%35) pts had stable disease, and 21 (%43) pts progressed. No complete response was seen. In responded pts, response durations were between 17–154 weeks (median 36 wks). After observation of mean 23 wks (range 1–164 wks) only 4 pts (%8) are stil alive. Mean survival was 23 ± 1.4 wks (%95 CI 20.3–25.8) and were between 1–164 wks. One-year survival was %17 (SE:5). Totally, 207 courses (median 4, range 1–13) were given. Tolerance to oral E therapy was very good. No grade III/IV toxicity was seen. In univariate analyses by log rank test, ECOG PS (0–1 vs 2–3), weight loss (< vs ≥%5), stage (limited vs extended), erythrocyte sedimentation rate (ESR) (< vs ≥30 mm/h), serum albumin level (< vs ≥3.5 gr.dl), addition of radiotherapy (RT) (–/+) and response to CT (–/+) were statistically significant ($p < 0.05$) as prognostic factors effective over survival. On the other hand, age (< vs ≥70), body mass index (BMI) (weak vs normal), hemoglobin (< vs ≥12 g/dl), LDH (≤470 vs >470 IU/L), delay in CT (≤ vs >2 wks) were not statistically significant. In multivariate analysis, ECOG PS ($p = 0.0014$), ESR ($p = 0.0068$), RT (+) ($p = 0.0012$) and response to CT ($p = 0.0009$) were still statistically significant.

Conclusion: Due to its easy application, good tolerability and efficacy, oral E can be preferred in SCLC pts, especially to whom standard IV CT could not be given because of several causes.

1073 PUBLICATION

Symptom control and clinical benefit in advanced non-small cell lung cancer: Early report of a randomized study of gemcicitabine monotherapy versus cisplatinum-vindesine

J. Vansteenkiste[1], J. Vandebroek, P. Weynants, L. Bosquée, R. Deman, D. Galdermans, J. Roelandts, Y. Valcke, P. Van Den Brande, W. Van Kerckhoven. [1]*Univ. Hosp. Leuven and coworkers of the Leuven Lung Cancer Group, Belgium*

Chemotherapy in advanced NSCLC results in a small survival benefit. More important is its role in symptom control and quality-of-life improvement. In phase II trials, single agent gemcitabine (GEM) showed to be active in NSCLC, with a clinical benefit or symptomatic response rate (RR) higher than the objective RR.

We initiated a prospective randomized trial to compare the objective RR and clinical benefit of cisplatinum-vindesine chemotherapy (PV) versus GEM monotherapy. Clinical benefit is scored by a patient visual analogue symptoms score, the evolution of the Karnofsky performance status (PS) and weight.

At the time of writing, 46 patients were randomized. Seventeen evaluable treatments were panel reviewed. For PV, we found 1 partial response (PR), 5 stable disease (SD) and 2 progressive disease (PD). For GEM this was 1 PR, 3 SD and 5 PD. Toxicity was analyzed in 53 cycles. The number of cycles with WHO grade III/IV toxicity in the PV arm was leukopenia 5, granulopenia 4, vomiting 2 and hair loss 3. For GEM, this was leukopenia 1 and diarrhoea 1 cycle. Clinical benefit was present in 2 PV patients (1 with objective PR, 1 with SD) and 3 GEM patients (1 with objective PR, 2 with SD).

Patients without objective response can nonetheless have clinical benefit from their chemotherapy. It is too early to draw further conclusions, but a trend towards lower objective RR and milder toxicity in the GEM arm is suggested. Updated results on a larger number of patients will be reported.

1074 PUBLICATION

Radiation related toxicity in patients with limited stage small cell lung cancer (SCLC) receiving irradiation on primary tumor site after intensive chemotherapy

Z.P. Mikhina[1], N.F. Orel[2]. [1]*Dept. of Radiology;* [2]*Dept. of Chemotherapy, Cancer Research Center RAMS, Moscow, Russia*

Purpose: In our past study 222 pts with limited SCLC received chest irradiation after standard chemotherapy. Acute radiation toxicity was 37.8%, pulmonary toxicity 80% and pulmonary fibrosis 83% at X-ray. In this study we evaluated the radiation related toxicity after intensive chemotherapy.

Methods: Fifty-three pts received local regional irradiation with doses 40–50 Gy after 2–3 courses of intensive chemotherapy with haematological support (ABMT – 14 pts, GM-CSF – 25 pts, polidan – 14 pts).

Results: Acute radiation related mucosal toxicity (oesophagitis, laryngopharyngitis) was seen in 59% of pts and pulmonary toxicity in 85% of cases at the period of time up to 3 months. The delayed local pulmonary fibrosis in the irradiation site was seen at X-ray in 85% of pts, whereas only 8% of them had clinical symptoms.

Conclusion: Pulmonary fibrosis did not worsened quality of life of pts with SCLC which was influenced mainly by the presence of residual tumor or local recurrence after CR and also by the presence of distant mts and is the same as in pts with standard chemotherapy. In pts with intensive chemotherapy was more acute radiation toxicity (59% vs 37.8%).

1075 PUBLICATION

Pair: Palliative accelerated irradiation regimen for non-small-cell lung cancer: Final results of the pilot study

U. Nestle, C. Nieder, K. Walter, S. Maubach, D. Ukena[1], M. Niewald, K. Schnabel. [1]*Dpt. of Radiotherapy and Pulmonology, Univ. Hosp. Homburg/Saar, Germany*

Purpose: In order to avoid overtreatment for patients with advanced non-small cell lung cancer (NSCLC) we have developed a palliative accelerated irradiation regimen (PAIR). Before the onset of a randomized trial in February 1994, we performed a one year pilot study testing the feasibility