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Weekly paclitaxel (W-PAC) as second-line therapy in cisplatin pretreated patients with advanced non-small cell lung cancer (NSCLC)

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Background: A growing number of patients, mainly cisplatin (C)-pretreated, require second-line therapy for NSCLC but the optimal treatment and appropriate criteria for pts selection are not yet defined. A second-line phase II study was conducted in C-pretreated pts with advanced NSCLC to evaluate the activity and toxicity of w-PAC.

Patients and methods: Fifty-three consecutive pts progressing after one front line C-based chemotherapy were enrolled. All pts had measurable lesions and ECOG PS 0-2. W-PAC was administered as 1-hour infusion at a dose of 80 mg/m2 for three weeks with one week off. Pts characteristics were: M/F 46/7; median age 62 yrs (30-75); stage IIIA-B/IV 8/44, local relapse 1; squamous/non-squamous histology 16/37; ECOG PS 0/1/2 22/25/6; weight loss Y/N 14/39. Pts with stage III and local relapse were also pretreated with thoracic radiotherapy. At least 48 pts were needed to test P0 =15% vs P1=30% response/disease stabilization rate (alfa 0.05, power 0.80).

Results: All pts were assessable for response, toxicity and survival. A complete response was observed in 1 pt, partial response in 7, for an overall response rate (RR) of 15%, (95% CI 5-25%). A stable disease (SD) was registered in 11 pts, for an overall clinical benefit (CB=RR+SD) of 36% (95% CI 23-49%). Toxicity was mild, with G3-4 neutropenia and thrombocytopenia in 6% and 2% of pts respectively. Non hematological toxicity was negligible. No patient- or treatment-related variable was significantly related to RR in multivariate analysis, with histology only approaching statistical significance (p=0.06) in favor of non-squamous tumors. CB was significantly higher in pts with non-squamous histology (p=0.02) and C-based therapy (p=0.01) responders. A favorable trend for CB was observed in pts with PS 0-1 (p=0.06). Median progression-free survival (PFS) was 7 months in responders and 4 months in pts with SD. PFS was significantly related with good PS (p=0.001), non-squamous histology (p=0.01), C-sensitivity (p=0.02) and absence of brain metastases (p=0.04) in the Cox model. Median overall survival was 8 months.

Conclusions: w-PAC has acceptable palliative activity and excellent tolerance in C-pretreated pts. Clinical benefit seems to be higher in pts with PS 0-1, non-squamous histology and first line C-based chemotherapy responders.

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Vinorelbine (VNB) and gemcitabine (gem) in unfit or elderly patients (pts) affected by advanced non small cell lung cancer (NSCLC): may sequential administration improve results ?

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VNB and GEM are the reference drugs in elderly or unfit NSCLC pts and may have a better toxicity profile with a sequential schedule: preclinical data (Brooks, AACR 2001) showed better citotoxic effects with VNB -(24 hours)- GEM sequence, rather then opposite one or same-day infusion. The pharmacologically-oriented combination of these different molecules might exert better results than empirical association. Based upon this premise, we enrolled in a phase II study, from 11/2001 to 07/2002, 27 pts affected by untreated NSCLC with locally advanced (5 pts stage IIIA, 8 stage IIIB) or metastatic (14 pts) stage, aged >70 years (21pts) or unsuitable to platinum treatment (6 pts). Mean age 72 years (62-80), M/F 26/1, ECOG PS 0-1-2 = 3-20-4, 12 adenoca., 9 squamous, 6 other, were main characteristics. Sequential administration consisted in VNB 25 mg/mq on days 1 and 8 as a 5-10 minutes bolus, followed by GEM 1000 mg/mq on days 2 and 9 as a 30-min. infusion, q.21 days. One hundred twelve cycles (cy) were administered, mean 4/pt; all pts are evaluable for toxicity and response, after a minimum of 3 cys. Toxicity issues were meaningfully mild (% of cy): WHO G IV neutropenia occurred in 4.5%; GIII neutropenia in 3%; GII anemia in 1% and G I thrombocytopenia in 10%. Non haematological toxicities were: no G III-IV, G II asthenia 1%, G I renal 2%, G I stomatitis 1%, G I emesis 3%. Myelosuppression was the most common cause of delays, but dose reductions and delays were uncommon: median duration of cy was 24 days and pts achieved 93% of planned dose intensity. Ten pts obtained a partial response (RR:37%) as follows: 2 pts stage IIIA, 6 stage IIIB, 2 stage IV; 12 pts had stable disease (44%), with symptoms improvement (fever, cough, shortness of breath) in most; 5 had progression. In our experience, the sequential drug administration maintained the activity of the combination, while markedly ameliorated the toxicity profile.

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Bronchoscopic radioisotope injection for sentinel lymph-node mapping in potentially resectable non-small-cell lung cancer

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Background: Prospective study to evaluate the feasibility of a preoperative bronchoscopic radioisotope application, followed by conventional sentinel lymph-node (SLN) identification, and to investigate the occurrence and distribution of micrometastases in relation to SLN activity.

Material and methods: 20 patients with a mean age of 63 years and proven clinical stage T1-3 N0-1 NSCLC were included. A dosage of 80 MBq radiolabeled technetium-99m nanocolloid was endoscopically administrated on intubated patients in the operation theatre. At thoracotomy, scintigraphic readings of both the primary tumor and hilar and mediastinal lymph-node stations were obtained with a hand-held gamma counter. Patients underwent lung resection and mediastinal lymphadenectomy. Radiolabeled nodes were also examined separately on back-table. SLNs were defined as the hottest nodes or nodes with at least one tenth of the radioactivity of the hottest nodes. SLNs pathologic assessment included standard examination using hematoxylin and eosin staining on step sections and immunhistochemistry (ICH) for cytokeratins.

Results: Identification of SLNs was possible in 19/20 (95%) patients after bronchoscopic radioisotope application. In 7/19 (37%) patients, a unique SLN was identified, whereas in 12/19 (63%) patients, nodes from 2 different stations could be classified as SLNs. Metastatic nodal disease was found in 9/19 (47%) patients. ICH revealed micrometastases in 2/12 (17%) patients initially classified nodal negative. Pathologic negative SLNs were a predictor for absence of metastatic nodal disease after mediastinal lymphadenectomy. No complication related to the procedure was observed.

Conclusions: Our preliminary results suggest that preoperative bronchoscopic radioisotope injection for sentinel lymph-node identification is a safe and simple method, improving accuracy of sentinel lymph-node detection in comparison to intraoperative technique. The absence of metastases in the SLNs seems to predict a negative nodal status accurately.

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Effects of concomitant cisplatin and normofractionated radiotherapy on inoperable non-small-cell lung cancer.

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Purpose: To evaluate normofractionated radiotherapy (RT) with combined chemotherapy in patients with inoperable non-small cell lung carcinoma (NSCLC).

Methods and Materials: From April 1995 through March 2002, 56 patients ineligible for available combined modality protocols in our institution were enrolled and treated with radiotherapy consisting of 60 Gy (50 Gy + 10 Gy Boost) given in 30 fractions of 2 Gy daily, 5 days a week, over a time of 6 weeks, and concurrent low-dose daily chemotherapy (CHT) consisting of 6 mg/m* of cisplatin given Mondays to Fridays during weeks 1-2 and 5-6. All patients had stage III disease. Age ranged from 39 to 81 years (median 63.9 years).

Results: The 2- and 3-year survival rates were 36% and 20%, respectively, with a median survival of 10.2 months. Patients with a pretreatment haemoglobin level superior or equal to 11.6 g/dl had a 2-year survival of 52% as compared to 15.5% for patients with a pretreatment haemoglobin level inferior to 11.6 g/dl (p = 0.0075). Patients with higher KI (>70%) did better than those with lower KI. Surprisingly, patients in stage IIIA did not significant better than those in stage IIIB.

Haematological toxicity (grade (*2)) prevailed (25%), followed by oesophageal (5.4%) and bronchopulmonary (2%) toxicity. Only three patients experienced acute Grade 3 haematological toxicity. Because of acute toxic effects, irradiation was interrupted in 8 (14.3%) patients for 713 days (median 7.5 days). Dose modifications were not made. Late high-grade (*3) toxicity was not found. No Grade 4 toxicities or treatment-related deaths were observed during this study.

Conclusion: The combined radiochemotherapy was well tolerated. We obtained the same good results with a normofractionated RT with fewer side effects than studies with hyperfractionated RT. The KI and the haemoglobin level at the start of the treatment seem to be the most relevant prognostic factors.

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Impact of third line ZD 1839 therapy on patients with advanced non-small cell lung cancer (NSCLC) who had failed prior platinum and/or docetaxel-based regimens (Astra Zeneca Expanded Access Programme)

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Background: Patients with locally advanced or metastatic NSCLC pretreated with two or three regimens of conventional standard chemotherapy have a median overall survival time of 4 months (Massarelli et al. Lung Cancer 2003). Iressa, an EGFR tyrosine kinase inhibitor, has recently shown a favourable overall tumor growth control (30%) and symptomatic improvement (40%).

Aim: The efficacy of a third line with ZD 1839 as an outpatient salvage treatment was analyzed on the basis of tumor response rates, time to third progression (TTTP), time to death (TTD) and disease-related symptom response.

Patients and Methods: 32 patients who had failed two previous chemotherapy regimens (median age 64; M/F, 69/31%; PS 1/2/3, 50/44/6%, locally advanced/metastatic disease, 69/31%) were treated with oral ZD 1839 250 mg/daily.

Results: An early tumor progression (TTTP <3 months) occurred for a minority of evaluable patients (4/24, 17%). A favourable overall tumor growth control was observed in 20/24 (83%) of the heavily pretreated patients, including partial remissions in 2/24 (8%) (both women with histologically confirmed adenocarcinoma) and stable disease in 18/24 (75%) patients. Median overall time to third progression and TTD evaluated from the beginning of the third line treatment on 13 evaluable patients were respectively of 4 and 6 months. Approximately 80% of patients (13/16) having a time to second progression not lower than 4 months with Docetaxel, had a TTTP with Iressa greater than 4 months. The majority of drug-related adverse events were mild and reversible. Grade 2/3 diarrhoea and skin rash required treatment's discontinuation in only 2 patients (8%). Performance status (Karnofsky Scale) scores decreased in 10/32 patients (31%), allowing to reduce the analgesic use.

Conclusion: Our experience confirms Iressa's activity and acceptable toxicity. A significant correlation was seen regarding second line treatment with Docetaxel and related time to progression. An updated efficacy and toxicity analysis will be presented at the meeting.

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Randomized trial of docetaxel plus cisplatin (DC)versus etoposide plus cisplatin (EC) in locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).

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Background: The aim of this study was to compare DC and EC regimens in terms of response rate, safety profile, and overall survival (OS).

Materials and Methods: From April 2000 to March 2002, 78 patients with locally advanced (LA, Stage IIIB), recurrent (R), or metastatic (M) NSCLC were recruited. Eligibility criteria included: age ≥ 18 years, pathologically confirmed NSCLC, no prior chemotherapy, Karnofsky performance score (KPS) ≥80%, measurable disease, no brain or leptomeningeal metastasis, and signed informed consent.

Patients:

	DC	EC
n	40	38
Median Age (years)	64.5	59.0
Adeno./ Squamous	47.5%/50%	50%/48.7%
LA/ M/ Local R	50%/47.5%/2.5%	42.1%/57.9%/0%
Prior RT/ Surgery (n)	1 /2	0/ 4
KPS	80	80

DC treatment consisted of 75mg/m^2 of both agents given on day 1, every 3 weeks for 6 cycles. EC treatment consisted of 75 mg/m^2 of cisplatin on day 1, and 100mg/m^2 of etoposide on days 1–3, every 3 weeks for 6 cycles.

Results: Thirty-four patients from the DC arm and 33 patients from the EC arm were included in the efficacy analysis. Two patients in the DC arm did not receive treatment; 1 patient withdrew consent and 1 developed brain metastasis. Four patients from the DC arm received the first cycle of treatment but could not be evaluated for response; 1 patient was lost to follow up (f/u), 2 withdrew consent, and 1 died as a result of an accidental fall. From the EC arm, 3 patients withdrew consent, 1 was lost to f/u, and 1 died of cardiac arrhythmias. Adverse events NCI grade ≥ 3 occurred in 32 patients (19 DC/13 EC): neutropenia 4(10.5%)/6(15.8%); febrile neutropenia 3(7.9%)/0; sepsis 1(2.6%)/0; infection 1(2.6%)/0; nausea 2(5.3%)/4(10.5%); diarrhea 2(5.3%)/1(2.6%); fatigue 3(7.9%)/0, alopecia 6(15.8%)/6(15.8%).

Conclusion: DC offers superior response rates over EC and shows a trend in improved median survival in chemotherapy-naïve patients with locally advanced (Stage IIIB), recurrent, or metastatic NSCLC. There was no significant difference in TTP between groups and both regimens were well tolerated.

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The placental growth factor (PlGF) gene is more highly expressed in small cell lung cancers compared to non-small cell lung cancers

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Background: The characteristics of SCLC are that they disseminate in their early stages to distant organs, and that they recur frequently despite initial high sensitivity to chemotherapy and radiation. Differences in the gene expression profiles in small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC) may explain their different clinical characteristics. The aims of this study were (1) to identify genes differentially expressed in SCLC and NSCLC using mRNA differential display, and (2) to determine the clinical relevance of such genes in lung cancer.

Material and Methods: RNA differential display using three SCLC and six non-SCLC cell lines was used to identify a differentially expressed gene. Differential expression of the gene was confirmed in additional lung cancer cell lines using RT-PCR. Immunohistochemical staining for the gene product was performed on paraffin-embedded tissue from lung cancer patients. We examined the relationship between the expression of the gene and clinical parameters, including disease stage, response to treatment and survival time.

Results: The PlGF gene was identified as preferentially expressed in SCLC compared with NSCLC cell lines using mRNA differential display. Further analysis of 45 lung cancer cell lines using RT-PCR showed that the PlGF gene was expressed in nine of 13 SCLC cell lines (69%) and five of 32 NSCLC cell lines (15.6%) ($P < 0.001$, Fisher's exact test). Immunohistochemistry using anti-PlGF antibody on the paraffin blocks from lung cancer patients showed that PlGF expression was significantly higher in SCLC than NSCLC tissue sections (32% vs 5.6%, $P = 0.041$, Fisher's exact test). Expression of PlGF protein did not correlate with disease stage, response to treatment or survival time in SCLC patients.

Conclusion: The present study suggests there is higher expression of PlGF in SCLC compared to NSCLC. It may be that higher expression of the angiogenic factor PlGF contributes to differences between the progression of SCLC and NSCLC, especially in regard to the nature of SCLC metastasis.

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Oral chemotherapy and upper gastro-intestinal tolerance (UGT) improvement of nausea and vomiting in non-small-cell-lung-cancer (NSCLC) patients (pts) treated with oral navelbine (NVB) and standard antiemetic prophylaxis

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Background: UGT during oral chemotherapy is a constraint which may limit its use in cancer pts. Oral NVB is a new formulation that allows a