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Post-induction FDG-PET in NSCLC IIIA and IIIB: Correlation with morphometric tumor response after docetaxel (D)/carboplatin (C) chemotherapy in combination with erythropoietin

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Objective: D/C combination chemotherapy (CTx) has shown high response rates in advanced NSCLC. Histologic tumor response after CTx as well as combined induction regimens are highly associated with systemic tumor control and potentially with cure. Metabolic tumor response by FDG-PET after induction CTx has been shown to be predictive of outcome in NSCLC. Finally, erythropoietin (EPO) may prevent the decrease of Hb-values (median of −2.7 g% in a previous study) and thus may increase efficacy of induction CTx. Therefore, the aim of the study was to correlate FDG-PET after D/C-EPO CTx with morphometry.

Patients and Methods: 38 NSCLC stage IIIA and IIIB pts were enrolled and received D 100 mg/m2 d1 and C AUC 7.5 d2 q21 days for 4 cycles. Epo was administered at a dose of 3 × 10,000 IU/week s.c. All pts. received adjuvant radiotherapy.

Results: Of the 38 enrolled patients, 28 are evaluable for response by CT-scan. 20/28 pts. (71%) achieved PR. 4 had SD and 4 PD (14%). 24 of 28 responders are evaluable for control-FDG-PET. 21/24 pts. (87%) had a decrease of SUV by >50%, 8/24 had a SUV < 2.5 (CR). Six of these 8 pts. have been resected and specimens were morphometrically analyzed. In all 6 cases, no vital tumor cells (regression grade III = morphometric CR, according to Thomas et al., JCO 2000) were identified in the specimens. In contrast to the previous study performed without EPO, Hb-levels increased by a median of 0.3 g%.

Conclusion: Morphometric regression grade III after induction CTx correlates highly with metabolic CR by FDG-PET. After a median follow-up of 21 months, all patients with CR by FDG-PET survived disease free. Thus FDG-PET may represent a non-invasive diagnostic tool to predict pathologic response and potentially long term outcome in stage III NSCLC.

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Continous accelerated hyperfractionated radiotherapy (CHART) plus chemotherapy (CT) with vinorelbine (VB) and cisplatinum (CDDP) in locally advanced NSCLC (TOG-011 study)

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Purpose: A phase II study was conducted to evaluate the efficacy and tolerability of CHART plus daily CDDP plus sequential CT with VB and CDDP.

Materials and methods: Patients histologically proven with NSCLC, stage III, less than 70 years old, whose performance status was 0-2 and who had no prior therapy were included. Twenty-two patients enrolled to the study. Their median age was 52 years old (31-70 years). Stage was 3B in 16 and 3A in 6 patients. Two cycles of VB 30 mg/m2 and CDDP 75 mg/m2 were given in 3 weeks apart. Then, patients were treated by CHART with CDDP as a radiosensitizer 6 mg/m2 (max. 10 mg) daily. 54 Gy in 36 fractions were given 3 times a day over 12 consecutive days. The dose per fraction was 1.5 Gy. Two cycles of CT were applied three weeks after CHART with the same schedule.

Results: All of the patients completed the therapy. At the end of the therapy there were 4 CR, 12 PR and 6 stationary diseases. Fifteen of the patients died and 7 patients were alive during evaluation. 3 of them were with disease (19, 25, 40 months) and 4 were without disease (15,10, 4, 4 months). Median local control duration was 10 months (6-22) and median survival time was 12 months (4-14) and 1-year survival rate was 47,6%. Median disease-free survival was 7 months (4-22). Distant metastases were found in 9 patients. Grade 1-2 toxicity in 18 patients and grade 3 toxicity in 6 patients were observed. Esophagitis was the most common side effect. Grade 1-2 dysphagia were seen in 13 patients and grade 3 dysphagia was observed only in 2 patients. Four patients developed grade 3 nausea and vomiting during CT. There was no serious hematologic toxicity due to CT. CDDP dose was reduced in two patients due to grade I nephrotoxicity. Five patients developed radiation pneumonitis and 7 had radiation fibrosis. They all recovered by medical therapy.

Conclusion: This combined modality regimen appears to improve the response rates and local control and median survival with mild toxicity.

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Final results of a phase II study of Gemcitabine (G) and Platin (P) in advanced non-small cell lung cancer (NSCLC): Long-term follow up and intention-to-treat analysis

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Introduction: G, a nucleoside analogue, has efficacy in BSCLC, with synergism or additive effect both *in vivo* and *in vitro* with P. We report final results of a prospective multicentric phase II study on the safety profile, clinical efficacy and survival obtained with our regimen G 1500 mg/m^2, administered as a 30' i.v. infusion on day 1 and 8, and P 100 mg/m^2 on day 8, given on 21-day cycle (c) (Ann Oncol 10 (5): 57–62, 1999). This regimen is different from Others's because of P was delayed to the 8th day and only 2 accesses/c.

Results: From Oct '96 to Feb '98, one-hundred-five consecutive untreated pts (90 M), cytological or hystological NSCLC proved, entered the study; median age 61 y.rs (34–78 y.rs); P.S. ECOG 0 in 57 pts, 1 in 41, 2 in 7; adenocarc. 39 pts, squamous cell 43, large cell 3, undiffer. 20; stage IIIa unresectable 13 pts, IIIb 29, IV 63 (5 pts with asymptomatic brain mts). Evaluable for response (at least 3 c.s) 88 pts [6 had very early PRO, 16 stopped therapy because of tox (creatinine ≥ 1.6 mg/dL - 4 pts, cutaneous tox after fast dose G - 2 pts, subjective intolerance - 2 pts) and 2 because of cardiac failure not drug related]. Compliance by pts was good. No death therapy related occurred. Thrombocytopenia (thrp) WHO g 3–4 in 9.6% and 6.7% courses and 5 pts received plts transfusion; 3–4 neutropenia 27.7%; 45.2% pts received prophylactic or on-schedule G-CSF; g 3–4 anemia in 18.3% and 1.9%, 17 pts requiring blood transfusion. Non-haematological tox, except for the above reported: g 1–2 long standing peripheral neuropathy 20.2%. Objective responses: CR + PR 45 (51%, 95% C.I. 40–62); SD 30 (34.1%, 95% C.I. 24–45). Median response duration 6.5 *mo.s* (95% C.I. 3.5–13).

In conclusion, present report shows a 43.3% RR (CI 95%, 33.7–52.8) and a median overall survival 12.1 mo.s (95% C.I. 9.9–13.5), on an intention-to-treat basis (all pts included). Thrp and financial costs was much lesser than in the 3 accesses/c Others's regimens with P given on day 2.

EOLO (Eastern Oncology Lung Organization). In praise of GOCNE (Gruppo Oncologico Cooperative Nord. Est), CRO-Aviano (PN), and AOI (Associazione Oncologica Italiana), Aviano (PN), Italy.

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Gemcitabine (G) with concurrent chest radiation (XRT) followed by consolidation chemotherapy with gemcitabine plus cisplatin (CDDP): a phase I trial for patients with stage III non-small cell lung cancer (NSCLC)

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We conducted a phase I trial to determine the maximum tolerated dose (MTD) of weekly G given concurrently with chest XRT for locally advanced NSCLC.

Eligibility: Medically inoperable stage II or stage III (except effusion) NSCLC, less than or equal to 5% weight loss, performance status 0-1 and no prior XRT or chemotherapy.

Treatment Plan: G weekly x 7 wks concurrent with chest XRT 63 Gy/35 fxs. Initial XRT used conventional 2D ports, but was modified to 3D conformal approach. With 3D XRT, G starting dose was 125 mg/m2/wk. 4 weeks after chemo/XRT is completed, patients receive consolidation chemotherapy consisting of 4 cycles of G at 1000 mg/m2/wk days 1, 8, and 15 plus CDDP 60 mg/m2 on day 1.

Results: With the initial study design of 2D XRT, dose limiting toxicity (DLT) of grade 3 esophagitis occurred in 3/6 pts at G 150 mg/m2/wk and 2/3 pts at G 125 mg/m2/wk. The protocol was thus amended to 3D conformal XRT. Using 3-D XRT, 0/3 pts who received G 125 mg/m2/wk and 0/3 at a G dose of 150 mg/m2/wk experienced DLT. At a G dose of 190 mg/m2/wk with concurrent 3D XRT, 2/6 pts had DLT of grade 3 esophagitis. There was a strong relationship between volume of esophagus in the XRT port and grade of esophagitis. Percent esophageal exposure at 60 Gy averaged 71% for the 2D cohort vs only 11% in the 3D cohort. With a median follow-up of 40 weeks, estimated median survival is 55 weeks and estimated 1-year survival is 53% [95% CI: 33%, 85%].

Conclusions: The MTD of G given weekly concurrent with conventional 2D XRT was less than or equal to 125 mg/m2/wk x 7wks. However, with 3D chest XRT the MTD was 190 mg/m2/wk x 7wks. DLT was grade 3 esophagitis. G given concurrently with 3D XRT is better tolerated than with 2D XRT, presumably due to decreased volumes of esophagus exposed using 3D approach.

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Weekly docetaxel as second line chemotherapy in advanced non small cell lung cancer (NSCLC): Final results and survival analysis

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The activity and toxicity of weekly docetaxel (D) after platin-based first-line therapy for advanced NSCLC were investigated in a prospective phase II study. A final analysis of 36 patients is presented.

Patients and Method: 36 patients were enrolled between 1/99 and 4/00. Most pts. (n = 26) showed progressive disease under first-line therapy. One third (n = 11) of pts. had a "sensitive relaps". Pts were treated with 6 cycles of weekly D (35 mg/m^2) each interrupted by a 14 days break. In total 3 courses were administered. A total of 222 infusions of docetaxel were administered (median 6 weekly infusions).

Results. *Toxicity:* Severe (grade III/grade IV) hematotoxicity was not seen. Other than one grade IV diarrhea, grade III non-hematologic toxicities included nausea (1), asthenia (1), spontaneous pneumothorax (2), fluid retention (1), arrythmia (1), and nail toxicity (1). Mild cutaneous and nail toxicity occurred in 29 pts, neutropenia grade II in 2 cases, and mild asthenia (grade I and II) in 48 courses. *Response:* 35 patients were evaluable for response. Partial response (PR) was observed in 4/35 (11%), stable disease or minor response (SD/MR) in 14/35 (40%), and progressive disease (PD) in 17/35 (49%). Three pts are still alive (censored 8.3%). Median survival was 160 days (115–205, 95% CI., Kaplan-Meier-analysis, 3 cases censored).

Conclusion: Weekly docetaxel (35 mg/m^2) as second line therapy is a well tolerated and safe regimen without occurrence of grade III/IV hematotocicity.

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Gemcitabine (GEM) and docetaxel (DTX) salvage regimen in non-small cell lung cancer (NSCLC) failing prior paclitaxel platinum-based chemotherapy

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Purpose: Treatment options in patients with recurrent NSCLC remain limited as a result of poor activity of older agents after platinum-based therapy. In the present phase II study we evaluated the combination of GEM DTX in relapsed NSCLC.

Methods: Patients with advanced NSCLC (stages IIIB/IV), WHO-PS-2, prior paclitaxel platinum-based chemotherapy, unimpaired hematopoietic and organ function were eligible. Chemotherapy was administered as follows: GEM 1000mg/m2 on days 1 8 followed by DTX 100mg/m2 on day 8, recycled every 21 days. Prophylactic G-CSF was administered from day 10-14 or until WBC 5.000/Zl.

Results: 43 patiens have entered; 41 were evaluable for response and all for toxicity: median age=63 (47-70), PS=1 (0-2), gender=38 males/5 females, stages IIIA=4, IIIB=17, IV=22. Metastatic sites included; lymph nodes: 28, bone: 6, liver: 5, brain: 5, lung nodules: 8, adrenals: 7, other: 3. All patients had prior paclitaxel platinum-based treatment; 28 patiens had prior paclitaxel-ifosfamide-cisplatin. Objective responses were; PR: 14/43 [33%; 95% confidence interval (CI)=18.5-46.6%], SD: 16/43 (37%; 95% CI=22.8-51.6%) and PD: 13/43 (30%; 95% CI=16.3-43.7%). The median time-to-progression (TTP) was 6mo (1-20) and median survival 8mo (1.5-20). 1-year survival was 28%. Grade 3/4 neutropenia was seen in 53% of patients (30% grade 4) and 14% incidence of febrile neutropenia. Grade 3 thrombocytopenia was seen in 7% of cases (no grade 4), while other grade 3 non-hematologic toxicities were never encountered.

Conclusion: The combination of GEM DTX is active and well tolerated in patients with advanced NSCLC failing prior taxane/platinum. It represents an effective combination to apply in the palliative treatment of relapsed NSCLC.

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Neoadjuvant chemotherapy followed by surgery in stage IIIa/IIIb non-small cell lung cancer

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Purpose: The study was undertaken to test whether marginally resectable or unresectable stage IIIa-IIIb non-small cell lung cancer (NSCLC) patients (pts) could reach a complete resectability after induction chemotherapy. The response to chemotherapy, surgical results and survival analysis were evaluated.

Methods: 56 pts were included into the study of Group A, vinorelbine 35mg/m2 day 1 and cisplatin 75 mg/m2 day 1; and Group B, vinorelbine 30mg/m2 day 1 and 8 and cisplatin 80 mg/m2 day 1. Cycles were repeated every 21 days. At the completion of induction therapy pts assessed to be resectable underwent thoracotomy. Radiation therapy was applicated in nonresected pts. The minimal follow up was 24 months.

Results: In our previous study, cisplatin and vinorelbine in the both dose intensity regimens proved to have a comparable toxicity and efficacy regarding response and survival. We report here the results of treatment for the entire group of 56 eligible pts. A total of 161 cycles were delivered. No complete response was observed. 30 pts (54%) had partial response, 15 pts (27%) had stable and 11 pts (19%) had progressive disease; 29 pts (52%) were surgically explored and 18 pts (32%) underwent a complete resection (pT0-3 N0-1). Complete pathological response was observed in 3 pts. In 6 pts lobectomy and in 6 pts pneumonectomy was done. 10 pts required intrapericardial pneumonectomy, with one tracheal, one esophageal and one chest wall resection. There were no lethal complications of surgery. The median survival of the whole group was 61 weeks. The cumulative survival was 59% at 1 year and 27% at 2 years. The median survival was 75 weeks in stage IIIa and 60 weeks in IIIb, the difference was not statistically significant. Responders survived significantly longer (93 weeks) comparing to pts with stable disease and progression (39 weeks, $p<0,001$). The completely resected pts survived significantly longer (122 weeks) as compared with the incompletely plus nonresected pts (50 weeks, $p<0,001$).

Conclusions: 32% of pts with marginally resectable or unresectable stage IIIa-IIIb NSCLC could reach a complete resectability after induction chemotherapy. Survival of pts stage IIIa was comparable to stage IIIb. Responders and resected pts survived significantly longer comparing to the pts with stable disease and progression, respectively to the incompletely resected plus nonresected pts. There were no treatment-related deaths in our study.

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A phase II trial of preoperative chemoradiotherapy using uft in clinical stage IIIb non-small cell lung cancer

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Purpose: Since our prior phase II trial showed the oral administration of UFT (Uracil + Tegafur) plus cisplatin with concurrent radiotherapy (60 Gy) in locally advanced non-small cell lung cancer patients to be effective (a response rate of 91%) and safe, we performed a phase II trial of preoperative treatment using this regimen.

Methods: From Sept., 1995 to Oct., 2000, 23 clinical stage IIIB patients were entered into this trial. Nineteen patients demonstrated T4N0-2M0 while 4 showed T1-2N3M0. UFT (400 mg/m2, p.o., d1-14, 29-42) plus cisplatin (80 mg/m2, i.v., d8, 36) were administered with concurrent radiotherapy (2 G/f. total 40 Gy).