168 POSTER

Chemotherapy followed by three-times daily hyperfractionated accelerated radiotherapy in stage IIIa (PN2)/IIIb non small cell lung cancer

T. de Pas[1], G. Catalano[2], U. Pastorino[3], F. de Braud[1], L. Spaggiari[3], G. Curigliano[1], B. Jereczek-Fossa[2], C. Robertson[4], R. Orecchia[2].
[1] European Institute of Oncology, Dept. of Medicine, Milan, Italy; [2] European Institute of Oncology, Dept. of Radiotherapy, Milan, Italy; [3] European Institute of Oncology, Dept. of Thoracic Surgery, Milan, Italy; [4] European Institute of Oncology, Div. of Epidemiology and Statistics, Milan, Italy

Introduction: No useful information is available on induction chemotherapy (CT) followed by three-times daily hyperfractionated accelerated radiotherapy (three fractions per day; hfRT) in locally advanced non-small cell lung cancer (NSCLC).

Patients and methods: Since February 1998, 49 patients (pts) with locally advanced NSCLC proved by mediastinoscopy entered a prospective study with induction CT followed by surgery, if suitable, and hfRT. Chemotherapy consisted in 3 cycles of cisplatin 80 mg/m2 d1 plus gemcitabine 1250 mg/m2 dd1,8 q3w (after cisplatin 100 mg/m2 d1 plus gemcitabine 1000 mg/m2 dd1,8,15 q4w was given to the first 10 pts all of whom required dose reduction/treatment discontinuation). Radiotherapy consisted of 54.4 Gy (1.2 + 1 + 1.2 die, 5 days/week) for patients treated with surgery and in 64.6 Gy (analogue fractionation) in all the others. Surgery was planned after CT in stage IIIa-pN2 patients with resectable disease.

Results: Chemotherapy obtained 75% response rate (95% CI: 57-87%) in 40 pts evaluable for response (9 pts: too early).

At present 28/36 pts staged IIIa-pN2 completed CT, 27 underwent surgery (R0: 24 pts) and 32 completed hfRT. With a median follow-up of 8.7 mths, 24 pts are alive with a 1 and 2ys survival estimated as 63% (95%C.I:47-85%) and 47% (95%C.I:29-79%), respectively.

All the 13 pts with stage IIIb NSCLC received hfRT: 12 completed the treatment and 9 pts died for disease progression with a median survival of 13 mths.

One postoperative death and 2 major surgical complication occurred. Three cases of RTOG grade 3 esophagitis were registered, with hfRT interruption in 1 case.

Conclusion: Induction chemotherapy followed by three-times daily hyperfractionated accelerated radiotherapy in locally advanced NSCLC is feasible and effective. Completion of the study and longer follow-up will be presented.

169 POSTER

A phase I/II study of twice-weekly gemcitabine and concurrent thoracic radiation for patients with locally advanced non small cell lung cancer (NSCLC)

A.W. Blackstock[1], G.J. Lesser[2], J. Fletcher-Steede[1], L.D. Case[2], R.W. Tucker[2], S.M. Russo[1], D.R. White[2], A. Miller[2]. *[1] Wake Forest University, Radiation Oncology, Winston-Salem, USA; [2] Wake Forest University, Medical Oncology, Winston-Salem, USA*

Introduction: 2'2'-difluoro-2'-deoxycytidine (Gemcitabine) is a fluorine-substituted cytarabine (Ara-C) analog that is an active agent in NSCLC and has significant radiation sensitizing properties. In an attempt to take advantage of its radiation sensitizing activity, we proposed a strategy to maximize the local radiation effect through the use of a concurrent twice-weekly gemcitabine schedule. Pre-clinical data from our laboratory and others, have shown that sensitization with gemcitabine is enhanced as the dosing frequency is increased. Therefore, we have attempted to determine the maximum tolerated dose (MTD) and efficacy of induction gemcitabine/carboplatin followed by twice-weekly gemcitabine and concurrent thoracic radiation in patients with stage IIIa/IIIb non small cell lung cancer (NSCLC).

Patients and Methods: 28 patients with histologically confirmed stage IIIa and IIIb NSCLC were studied. Patients received induction gemcitabine (1000 mg/m2) and carboplatin (AUC 5.0-5.5) for two - 21 day cycles. This was followed by escalating doses of gemcitabine administered via a 30 minute intravenous infusion twice-weekly for six weeks concurrent with 60-74 Gy of thoracic radiation. All thoracic radiation was delivered using 3-dimensional treatment techniques.

Results: Of the 28 patients entered, 17 were entered during the phase I portion of the study. The dose-limiting toxicity of twice-weekly gemcitabine was observed at 50 mg/m2 given twice-weekly (100 mg/m2/wk) and was grade III pneumonitis observed in one patient, grade III pulmonary fibrosis in a second patient and grade IV esophagitis observed in 2 additional patients. Twice-weekly gemcitabine at a dose of 35 mg/m2 was determined to be the MTD. The overall response rate for the 16 evaluable patients treated on the phase I was 88%. Toxicities observed for the 11 patients receiving induction and concurrent therapy was primarily neutropenia and thrombocytopenia. The median survival for the patients treated on the phase I portion of the study is an encouraging 16.0 months.

Conclusions: The maximum tolerated dose of twice-weekly gemcitabine is 35 mg/m2 (70 mg/m2/wk) given concurrent with thoracic radiation. These preliminary data would suggest this is an active regimen for the treatment of locally advanced NSCLC. A multi-institution Cancer and Leukemia Group B (CALGB) phase II study to ascertain the potential efficacy of this regimen is in development.

170 POSTER

Taxol-gemcitabine-vinorelbine (TGV) given every 2 weeks in chemo-naive advanced NSCLC. A SICOG phase I study

G. Frasci, G. De Cataldis, V. Lorusso, P. Comella, L. Maiorino, E. Crucitta, G.P. Nicolella, N. Panza, M. De Lena, G. Comella. *SICOG c/o INT, Naples, Italy*

Background: In a previous dose-finding study we selected the MTD of paclitaxel (T) (70 mg/sqm) when given with fixed doses of gemcitabine (G) (1,000 mg/sqm) and vinorelbine (V) (25 mg/sqm) on d 1&8 q3wk in advanced NSCLC patients. (Lorusso et al. ASCO 2000; 19:527a).

Purpose: To determine whether a higher dose intensity of gemcitabine and paclitaxel could be delivered by using an every-2 week schedule.

Patients and Methods: Chemonaive patients (pts) with locally advanced or metastatic NSCLC, age 18-70, and ECOG PS 0-2 were eligible. V was given every 2 weeks at a fixed dose of 25 mg/sqm, together with G and T at starting doses of 1,000 mg/sqm and 80 mg/sqm, respectively. G and T doses were escalated alternately by 250 mg/sqm and 20 mg/sqm respectively, until DLT occurred at cycle I in more than 33% of patients of a given cohort.

Results: As of April 5, 47 pts (median age 62; M/F = 38/9; stage IIIB/IV= 15/32; PS 0-1/2= 28/19) have been accrued, through 8 different dose levels, for a total of 153 cycles delivered. Doses of G and T of 1,500 mg/sqm and 150 mg/sqm have shown to be well tolerated (only 1 case of lack of hematologic recovery on d 15 at cycle I). Since we have considered the dose intensity of these 2 drugs satisfactory, we have decided to increase the dose of vinorelbine by 5 mg/m2 at each step. Two step have been completed in this way (vinorelbine 30 mg/m2 and 35 mg/m2), without encountering severe hematologic and nonhematologic toxicity. If all the 153 delivered cycles are considered, grade 3-4 neutropenia and thrombocytopenia have occurred in 18(39%) and 5 (11%) pts. Red blood cell transfusions have been required in only 4 patients. Fatigue, constipation, and peripheral neuropathy have been the most common nonhematologic side effects, although only 4 patients have shown severe nonhematologic toxicity. Nausea and vomiting have been generally mild. Thirty pts. are presently evaluable for response. One complete and 10 partial responses have been recorded for a 37% ORR.

Conclusion: The adoption of an every-2 week schedule allows the delivery of a higher dose-intensity of paclitaxel, and gemcitabine without impairing the tolerance of the treatment. The accrual still continues to define the MTD of vinorelbine, and we expect that the final results of the dose escalation will be available at the time of the meeting.

171 POSTER

Use of 3-dimensional conformal radiation therapy (3DCRT) for radiobiologically escalated dose for non-small-cell lung cancer (NSCLC)

P. Thirion, C. Mc Gibney, O. Holmberg, M. Pomeroy, J. Armstrong. *St. Luke's Hospital, Radiotherapy Department, Dublin, Ireland*

Rationale: Local control in patients (pts) with unresectable NSCLC has to be improved. 3DCRT allows dose escalation by sparing normal tissues, but to date most of the trials have increased dose by prolonging treatment duration. The enhancement of therapeutic ratio may be wasted by excessive treatment duration allowing tumour repopulation. We postulated that the therapeutic ratio of 3DCRT could permit dose and time escalation by increasing the fraction size (fr).

Aim: To assess the feasibility of a hypofractionated accelerated high-dose radiotherapy regimen (72 Gy/24 fr, 3 Gy/fr). Its biological effects are compared to a standard treatment in Table 1.

Methods: There were 15 pts with a histologically or cytologically proven NSCLC with KPS>70% and weight loss <10% in 3 months, with stage I/II medically inoperable (n=5) or stage IIIa/b without pleural effusion (n=10). Induction chemotherapy was used in 6 pts. The mean treatment time was 34 days (30 to 41). No more than 30% of the combined lung volume received more than 25 Gy and the maximum dose to the spinal cord was < 61%.

Results: No grade 4 acute toxicity (RTOG/SWOG scales) event was reported. 1 pt had a 1 week treatment break because of a grade 3 oesophagitis. With a 6.5 months follow-up, Grade 2 long-term oesophageal toxicity occurred in 2 pts. 1 pt died from massive haemoptysis not scored as treatment-related death. 13 pts were evaluable for tumour response. 6 complete and 3 partial response, 2 stable and 2 progressive disease occurred.

Table 1: Biological effect of the experimental and standard regimen

	Experimental Regimen	Standard Regimen
Total Dose/Number of fr	72 Gy/24 fr	60 Gy/30 fr
BED (acute effect/anti-tumour effect)*	102	77
BED(long-term effect)**	137	78
Overall treatment Time (weeks)	5	6

BED denotes for Biological Effective Dose, Gy for Gray, * alpha/beta ratio = 7, ** alpha/beta ratio = 3.3

Conclusions: More data are needed to confirm the feasibility of this strategy, but early toxicity data and tumour response rate are encouraging. This radiobiologically intense high-dose accelerated strategy also has practical and economical advantages

172 POSTER

Gemcitabine-cisplatin (GP) vs gemcitabine-carboplatin (GC) in advanced non-small cell lung cancer (NSCLC): a multicenter phase II randomized trial

P. Mazzanti[1], C. Massacesi[1], R. Mattioli[2], R. Trivisonne[2], F. Buzzi[2], G. De Signoribus[2], G. Tuveri[2], G. Rossi[2], L. Di Lullo[2], M. Bonsignori[1]. [1]*Medical Oncology Department, Ospedale Umberto I, Ancona, Italy;* [2]*for "Adria Medica " Study Group, Italy*

Background: In this randomized study we explored a 21-day schedule of both GP and GC regimens to assess toxicity and activity in advanced NSCLC patients (pts).

Patients and Methods: From Jan 1998 to Mar 2001, 115 untreated IIIB-IV NSCLC pts were randomized either to GP (62 pts) or to GC arm (53 pts). Before randomization, pts were stratified according to stage (IIIB vs IV) and PS (ECOG 0-1 vs 2). Treatment consisted of G 1.2 gr/sqm, d 1,8; P 80 mg/sqm or C AUC 5, d 2; every 21 days. Response rate (RR) was calculated according to the intent-to-treat principle. We utilized the Kaplan-Meier product-limit method to estimate time to progression (TTP) and overall survival (OS) rates.

Results: Characteristics of pts were as follow: median age 63 (40-75); M/F ratio 90/25; PS 0/1/2 in 24/71/20 pts; stage IIIB/IV in 45/70. Among pts with stage IV disease, metastatic sites were: bone 46%, lung/pleura 40%, adrenals 26%; distant nodes 18%, liver 13%, asymptomatic CNS 7%; others 7%; more than or equal to 2 sites in 26 (37%) pts. To date 36/115 pts are still alive, with a median follow-up of 11 months (mo). A total of 499 courses were delivered (262 GP, 237 GC), with a median number of 4 (1-6). All pts were evaluable for toxicity, 107 for response. WHO recorded toxicities at each course were generally moderate and overlapping for the two arms, except for: G1-2/G3-4 thrombocytopenia in 26/15 pts with GP and 15/5 with GC; G1-2/G3-4 leucopenia in 55/4 GP and 19/3 GC; G1-2/G3-4 emesis in 71/12 GP and 28/5 GC; G1-2/G3 peripheral neurotoxicity in 27/2 GP and 3/0 GC; G1/G2 renal toxicity in 13/2 GP and 1/0 GC; G1-2/G3 hair loss in 23/1 GP and 11/0 GC. Responses were as follows: 37 PR (23 in GP arm, 14 in GC) for an overall RR of 35%, 41% and 26% in GP and GC arm respectively. We observed a RR of 40% for pts with stage IIIB, and 27% with stage IV. Thirty seven (35%) pts had SD, with 20 (19%) lasted more than 6 mo, and 33 (30%) pts progressed. Median response duration was 7 mo (3-30+), (GP, 7 mo; GC, 6 mo). Median TTP and OS was 5 and 11 mo respectively. Although not directly comparable, we observed a higher TTP and OS in GP arm (7 and 11 mo respectively) than GC arm (5 and 10 mo).

Conclusions: Data of this study indicated both these 21-day regimens effective in advanced NSCLC. GC had a more favourable toxicity profile, but a possible higher activity was suggested for the GP regimen. Final results will be presented.

173 POSTER

A randomised phase II study of gemcitabine/cisplatin alone and with herceptin in patients with HER2-positive non-small cell lung cancer (nsclc)

U. Gatzemeier[1], G. Groth[1], V. Hirsh[2], C. Butts[2], N. Van Zandwijk[3], F. Shepherd[2], R. Rosso[4], J. Howell[5]. [1]*Krankenhaus Grosshansdorf, Department of Thoracic Oncology, Grosshansdorf, Germany;* [2]*McGill University Montreal, Cross Cancer Institute Edmonton, Princess Margaret Hospital Toronto, Canada;* [3]*The Netherlands Cancer Institute, Amsterdam, The Netherlands;* [4]*Istituto Scientifico dei Tumori, Genova, Italy;* [5]*Roche Products Ltd, Welwyn Garden City, UK*

Herceptin has demonstrated improvements in survival and time to progression when added to chemotherapy in treating HER2-positive breast cancer. Improvements in treatment for NSCLC are needed and some lung cancers do show HER2 positivity. A randomised phase II study recruited 103 patients with stage IIIB-IV NSCLC. Median age was 59 and 72% of patients had adenocarcinoma. Patients were all HER2-positive as measured by immunohistochemistry (2+, 3+), FISH or high serum HER2 levels (>15ng/mL). Approximately 4% of patients were positive by high serum HER2 only. Patients were randomised to treatment with gemcitabine (1250mg/m2 days 1+8) and cisplatin (75mg/m2 day 1) 3 weekly cycles (control) or gem/cis 3 weekly cycles plus Herceptin (2mg/kg) weekly.

Patients in both the control and Herceptin arms have received a median of 6 cycles of therapy. The incidence of grade III/IV toxicity in the control vs Herceptin arms was: nausea, 52 vs 47%; stomatitis, 6 vs 6%; asthenia, 12 vs 13%; headache, 16 vs 32%; anaemia, 12 vs 16%; thrombocytopenia, 35 vs 36%; and leucopenia, 37 vs 34%. Clinically significant cardiac adverse events were limited to 2 patients (1 grade IV, 1 grade V) in the Herceptin arm.

Investigator-assessed response rates in the control/Herceptin arms were (95%CI) 41% (28-56) and 32% (20-47), respectively. Median TTP was (months; 95%CI) 7.2 months (6.4-9.7) and 6.3 months (5.5-7.2), respectively. Overall, there were 7 FISH-positive patients and 5 of these responded to treatment. Time to progression in the control arm patient was 5.4 months and in the Herceptin arm patients 4.6, 8.5, 9.6 and 11.1 months.

Herceptin and gem/cis appears to be a well-tolerated regimen. There was no evidence in this study that Herceptin adds to the efficacy of gem/cis in NSCLC. In the small numbers of patients who were FISH-positive and treated with Herceptin, the TTP was generally longer than the median. However, the majority of tumours were moderate overexpressors (90% 2+ by IHC) and a benefit in patients whose tumours overexpress/amplify HER2 at very high levels cannot be excluded.

174 POSTER

HER2 status in non-small cell lung cancer (NSCLC): results from the patient screening for enrolment to a phase 2 study of herceptin

P. Heinmoeller[1], C. Gross[1], C. Schmidtgen[1], K. Beyser[1], C. Nordhoff[1], A. Bockholt[1], M. Pedrocchi[2], J. Rueschoff[1]. [1]*Klinikum Kassel, Institut of Pathology, Kassel, Germany;* [2]*Hoffmann-La Roche, Basel, Switzerland*

Purpose: Lung cancer is the major cause of cancer-related death in North America and Europe. About 75% of lung cancer is non-small-cell lung cancer (NSCLC). Overexpression of HER2 is associated with poor prognosis in NSCLC. The objective of this phase 2 study was to explore whether treatment with Herceptin would benefit patients with advanced NSCLC. For the enrolment in the pivotal Herceptin NSCLC trial patients were screened for HER2 overexpression at the 2+ or 3+ level by immunohistochemistry (IHC), and/or HER2 gene amplification of >2 by fluorescence in situ hybridization (FISH) and/or for shed antigen concentration >15 ng/mL by enzyme-linked immuno sorbent assay (ELISA).

Methods: 568 advanced and/or metastatic non-small cell lung carcinomas of stage IIIB and IV were evaluated. Of these 568 tumours, 164 were adenocarcinomas, 76 squamos cell carcinomas, 49 not further characterized large cell carcinomas, 2 signet ring carcinomas, and 279 tumours NSCLC not otherwise specified. 374 of the above tumours were examined with all three techniques.

Results: Adenocarcinomas were more frequently HER2 positive by IHC than squamous cell carcinomas and large cell carcinomas (31% vs. 19% vs. 14%, respectively). The HER2 gene amplification rate was low in all three tumour types (3.4% vs. 0% vs. 2.7%). Serum levels of >15 ng/mL were evident in 12 (19%) adenocarcinomas, 2 (3%) squamos cell carcinomas, and 5 (14%) large cell carcinomas. Out of 35 HER2 positive adenocarcinomas (by at least one method), 26 (74%) were poorly differentiated (G3). Overall, 29% of the evaluated tumours showed a positive HER2 status by at least one