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

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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.

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

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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

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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

of the three techniques. Other researchers reported HER2 overexpression in about 15% of NSCLC although the frequency may be as high as 34% in adenocarcinomas. Amplification of the HER2 gene could be demonstrated in only 2% of the tumours, while 22% were positive by IHC and 9% by ELISA.

Conclusion: In contrast to breast cancer, where IHC overexpression is closely related to amplification (>95% concordance), this is only the case in 8% of NSCLC. Shed antigen did not correlate with the cellular assays. These discrepancies suggest a different mechanism leading to a less pronounced overexpression, which may imply a different reactivity to Herceptin than in mammary tumour cells.

175 POSTER

Could endobronchial brachytherapy (EBBT) be a curative treatment ?

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Rationale: palliative effect of EBBT is actually well demonstrated. But its curative value is still unknown. We have reviewed our experience of EBBT in a very selected group of patients (pts) treated in a curative intent.

Selection criterias: pts with a localized endobronchial lesion, not visible on CT-scan, and without nodal or visceral metastasis. The tumor could occurred in a previously irradiated area.

Population: 100 pts fullfilled the selection criteria (Male: 92; median age: 59 yrs). Indication for EBBT were: relapse after surgery: 33; relapse after external irradiation (ERT): 37; chronic respiratory failure, contraindicating surgery or ERT: 25; others: 5.

Results: A complete response was obtained in 69 pts (69%), with, among them, 49 confirmed histollogically; partial or no response: 14 pts; unknown response: 17. Median, 1-yr and 3 yr survival were respectively 21 mths, 64% and 33%. Pts with a complete response had a better survival than the others (at 2 yrs: 55% vs 2%; p= 0,003). Pts with a lesion occurring in a not previously irradiated area had also a better response rate (p= 0.02) and a better survival (median survivals: 40 mths vs 12 mths; p = 0,001).

Conclusion: our study demonstrate the curative potential of EBBT with one third of the patients treated in a curative intent alive at 3 yrs. Major prognostic factors were response to EBBT and lesion occurring in a not previously irradiated area.

176 POSTER

Practical approach to patients presenting with multiple synchronous suspect lung lesions. A reflection on the current TNM classification based on 54 cases with complete follow-up

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Purpose: To examine the survival after surgical treatment of patients presenting with two synchronous suspect lung lesions, and to evaluate the actual TNM-classification, which has upgraded patients with two malignant lung lesions of the same histology into the T4 (both lesions in the same ipsilateral lobe) or M1 (different lobes of lungs) category.

Methods: Retrieval of all consecutive patients with two synchronous suspect lung lesions in the prospective database of the Leuven Lung Cancer Group in the interval between 1990 and 1994 (to allow complete 5-year follow-up data). Analysis of characteristics and survival data of all patients, who underwent surgical resection with intention to cure for both lesions.

Results: Forty-eight of 54 patients had surgical resection with curative intent. Their 5-year survival rate was 41%, with a median survival of 44 months. At postoperative histological examination, 30 patients proved to have two synchronous malignant lesions of the same histology. Their 5-year survival was 35%, with no obvious differences in survival between patients with two lesions in the same or in different lobes.

Conclusion: An aggressive surgical approach in carefully selected patients presenting with two suspect pulmonary lesions is rewarding. There is no doubt that patients with two malignant lung tumours of the same histology certainly have a higher disease stage than those with a single lesion, but the current stage IIIB or IV classification might underestimate their prospects for long-term survival after radical resection.

177 POSTER

Clinical characteristics, treatment, and prognosis of lung cancer elderly patients

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Background: Cancer in the elderly is becoming a complex and frequent issue to deal with. Increasing age is the major risk factor for the development of cancer, with approximately 60% of cases being diagnosed after the age of 65 years. The purpose of this study was to delineate any possible clinical difference between elderly and younger patients with lung cancer (LC). All patients seen for a newly diagnosed LC from 1/1/1983 to 31/12/2000 were the object of this study.

Methods: Anthropometric, anamnestic, clinical, laboratory, bronchoscopic, radiological, and pathological features (in all 74 variables) were prospectively recorded in 1464 patients during the period of time considered. Patients were divided according to their age at diagnosis (up to 69 years, GROUP 1, 70 years or older, GROUP 2). The 2 groups were compared, as appropriate, by the Student-t-test, the median test, the chi-squared test, the log-rank test for survival, and the Cox's regression analysis. The Bonferroni correction for multiple tests was applied.

Results: In all, we found 410 elderly patients (28% of the cohort). The following variables were different in the two groups examined ($p < 0.001$): smoke (sigarettes per day), weight loss, performance status, haemoglobin, platelet count, serum level of glutamic pyruvic transaminase, alkaline phosphatase, creatinine, and tissue polypeptide antigen. Also histologic subtype, and treatment modalities differed significantly. Survival was worse in older than in younger patients (39 weeks vs 29.7, $p < 0.001$). A Cox's proportional hazards regression analysis selected as prognostically significant: 1) KPS; 2) treatment; 3) N factor; 4) TPA; 5) weight loss; 6) neutrophil; 7) sodium; 8) creatinine; and 9) LDH.

Conclusion: Based on these findings, we conclude that no major tumour characteristic is age-dependent, and that patients' age is not an independent prognostic factor.

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Docetaxel and carboplatin combination as second-line treatment in metastatic non-small-cell lung cancer(NSCLC)

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Purpose: To evaluate the efficacy of the combination of docetaxel 75 mg/m2 and carboplatin AUC 6 mg/ml.min in pts with NSCLC who failed, or relapsed after previous chemotherapy. Second-line chemotherapy in NSCLC is only recently explored, since docetaxel has shown promising activity with improvement in survival and quality of life. Therefore, we investigated if a docetaxel-platinum combination could improve therapeutic efficacy in patients (pts) with NSCLC.

Patients and Methods: Pts were included with a diagnosis of stage IIIb/IV NSCLC, previous treatment with chemotherapy, PS $\simeq$ 2, and adequate bone marrow, liver and renal function. Treatment was administered every 3 weeks to a maximum of 5 cycles (cy).

Results: From January 1999 till December 2000 50 pts were included: 30 male and 20 female, median age was 56 yrs (range 30-76), stage IIIb/IV in 6/44 pts, PS 0/1/2 in 14/29/7 pts, adeno/squamous/large cell carcinoma in 23/19/8 pts. Prior treatment was gemcitabine in 2 pts, epirubicin-gemcitabine in 29 pts, and cisplatin-gemcitabine in 19 pts. Six pts had received additional high-dose thoracic radiotherapy. Median interval from prior treatment was 20 wks (range 2-100). Median number of cycles was 4 (range 1-5), 18 pts (36%) received the maximum number of 5 cy. Reasons to stop treatment earlier were disease progression in 16 pts, own request after 4 cy in 4 pts, hematological toxicity in 6 pts, non-hematological toxicity in 3 pts, and early death in 3 pts. Hematological toxicity (total of 176 cy) was CTC grade 3/4 (%cy): leukocytopenia 38/11, granulocytopenia 35/28, thrombocytopenia 9/3. Febrile neutropenia occurred in 4 pts; 2 pts died of sepsis. Non-hematological toxicity was mild, except fatigue CTC grade 3/4 in 5/1 pts. Blood and platelet transfusions were given in 19 and 4 pts, resp. Best tumor responses were: 17 PR, 19 SD, 14 PD. Overall response rate is 34% (95% CI 22-45). Four tumor responses (21%) were observed in pts after previous cisplatin-based treatment, compared to 13 (41%) in the non-platinum containing regimen. Median time to progression was 17 wks (95%CI 7-26), median survival was 29 wks (95%CI 22-36).

Conclusion: In pts with advanced NSCLC the combination of docetaxel with carboplatin is active as second-line treatment after prior gemcitabine-based chemotherapy with or without cisplatin, suggesting non-cross-resistance.