NSCLC. We conducted a prospective multicenter randomized phase III study with survival as primary endpoint. From June 1995 to Oct. 1997, a total of 210 patients (pts) were accrued to the trial; 104 were randomized to CC arm; CDDP 80 mg/m^2 on day 1 and CPT-11 60 mg/m^2 on days 1, 8, 15 q 4 weeks 106 to the control CV arm; CDDP 80 mg/m^2 on day 1 and VDS 3 mg/m^2 on days 1, 8, 15 q 4weeks. All pts were previously untreated, ECOG PS 0-2 and stage IV or Stage IIIB, with no symptomatic brain metastases. Both arms were well-matched with regards to sex, age, stage and PS. 199 pts were assessable for the response and toxicity. Stage IIIB: 41%, Stage IV: 59%, PS 0-1: 95%, PS 2: 5%. The objective tumor response was similar in both treatment groups, with 29% partial response (PR) in the CC pts and 22% PR in the CV. The incidence of grade 4 neutropenia was significantly higher in the CV than in the CC (18% vs 50%; P < 0.001). Conversely, the incidence of grade 3 or worse diarrhea was higher in the CC than in the CV (13% vs 1%; P < 0.001). The incidence of other toxicity was similar in the two groups. Median survival time was 45.4 weeks for CC, 49.9 weeks in CV (p = 0.786). The preliminary results suggest that the both groups are active combination in advanced NSCLC with similar response rate and survival.

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Pre-operative serum levels of angiogenic tumour markers in non-small cell lung cancer and its impact on survival

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Purpose: Angiogenesis is an important step in the progression of tumours. Several angiogenic factors have been discovered so far and two of the most studied are bFGF and VEGF. Indications are that both might have prognostic information concerning metastasis and survival. Yet, earlier studies of these angiogenic factors in sera have not been conclusive concerning prognostic information.

Patients and Methods: Our group have analysed the levels of bFGF and VEGF in preoperatively collected sera from 58 patients with a histo-pathological verified diagnosis of non-small cell lung cancer, limited disease. A semi-quantitative enzyme linked immunosorbent assay were used for detection of bFGF and VEGF. A cut-off level at the 95 percentile of a normal control subject group both for VEGF and bFGF were estimated at 500 pg/ml and 7.25 pg/ml, respectively.

Results: VEGF; Pre-operative levels of VEGF in sera were detected in all patients (median value 304 pg/ml, range 93–1554 pg/ml), 12 patients had elevated levels as defined by the cut-off level. Pre-operative levels of VEGF proved to be significantly correlated to survival, both as a continuos variable and when cut-off level were used (p-value = 0.006). In univariate analysis relapse was significantly correlated to high levels of VEGF (p-values < 0.05). bFGF; Pre-operative levels of bFGF in sera were detected in 56 patients (median value 4.60 pg/ml, range 0–43.02 pg/ml), 18 patients had elevated levels as defined by the cut-off level. When used as a continuos variable a significant correlation (p-value = 0.0028) could be demonstrated regarding survival.

Conclusion: Both bFGF and VEGF proved to have statistical significant association to survival in patients with non-small cell lung cancer.

991 POSTER

Genetic polymorphisms of cytochrome P4501A1 and glutathione S-transferase M1: A lung cancer case control study

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150 lung cancer patients and 300 age and sex matched control subjects have been examined for the association between polymorphisms of the CYP1A1 gene and homozygous deletion of the GSTM1 gene and lung cancer risk among Caucasians.

Methods: The CYP1A1 polymorphisms were detected by PCR/RFLP using DNA from peripheral white blood cells: the mutation m1 (MspI polymorphism in the 3'flanking region), m2 (BsrDI polymorphism in exon 7) and m4 (BsaI polymorphism is located two bp upstream from m2). GSTM1 genotype has been analyzed by PCR. Differences between groups were calculated by using Pearsons chi-square test.

Results and Conclusion: We could not find any significant difference between patients and controls for the homozygous and heterozygous MspI polymorphism. In contrast cases with heterozygous BsrDI polymorphism were at greater risk for adenocarcinoma (OR: 2.50; CL: 1.19–5.24; P < 0.01). The BsaI polymorphism was higher in control subjects than in patients and may therefore not represent a susceptibility factor for lung cancer. Our results show no influence of GSTM1 null genotype for lung cancer risk (OR: 1.04; CL: 0.69–1.57). Recruitment for this study is ongoing in order to further verify the obtained data.

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992 POSTER

Æ-941, an inhibitor of angiogenesis: Rationale for development in combination with induction chemotherapy/radiotherapy in patients with non-small-cell lung cancer (nsclc)

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Æ-941, a standardized shark cartilage extract, shows antiangiogenic and antimetalloprotease activities in vitro and ex ovo. It was selected by the US National Cancer Institute for phase III clinical evaluation of its efficacy and safety in advanced NSCLC patients. This double-blind placebo-controlled study will evaluate the effect on survival of treatment in inoperable stage III patients. The preclinical rationale for this study is based on the antimetastatic activity of Æ-941 in the Lewis Lung Carcinoma mouse model where a 70% reduction in pulmonary metastases was observed. Æ-941 was additive to cisplatin in reducing the number of lung metastases (83% reduction in combination compared to 54% with cisplatin alone). No mortality and no loss of body weight were observed at 500 mg/kg, the highest dose administered. Toxicology studies demonstrated no dose-limiting toxicity or target organ. The clinical rationale to support this phase III trial is based on the safety profile and clinical benefit obtained in the following studies. During a phase I/II study, 80 refractory lung cancer patients (64% with distant metastases) received Æ-941 in monotherapy (5 to 95 mg/kg/day orally). Patients receiving Æ-941 at 240 ml/day showed greater clinical stability in analgesics consumption and weight loss compared to patients during the first 12 weeks. Additionally, 72 refractory prostate cancer patients received Æ-941 in monotherapy in this study. No serious adverse events were observed in these two cohorts; seven percent of non-serious adverse events were related to Æ-941, most commonly nausea, vomiting. In another study, 61 patients received Æ-941 in combination with chemotherapy and/or radiotherapy. No serious adverse events occurred with Æ-941 in this cohort. In all clinical studies involving 375 patients (194 treated >3 months), only one drug-related serious adverse event was reported (hypoglycemic episode in a type II diabetic patient with renal cell carcinoma). Based on the potential antimetastatic activity of Æ-941 demonstrated in the Lewis lung cancer model, the excellent clinical safety profile and the preliminary dose trend observed, it is proposed to evaluate the effect of Æ-941 on survival in a randomized double-blind placebo-controlled clinical study in patients with locally advanced disease receiving induction chemotherapy and radiotherapy.

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Phase II study of gemcitabine (G) and cisplatin (P) in advanced nsclc. Focus on quality of life (QoL)

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The combination of G and P has been shown to be active in advanced NSCLC but the impact of this regimen on QoL is not well established. Aim of study was to evaluate this regimen in terms of both, toxicity, activity and its effect on QoL Eighty pts with advanced NSCLC (68 men and 12 women, median age 61 years, range 40–75, median PS 80, range 60–100, 40 stage IIIB and 40 stage IV) received G (1000 mg/m^2, d. 1, 8 and 15) and P (100 mg/m^2, d. 2); q 28 d. QoL was assessed with the EORTC QLQ-30 and LC-13 questionnaires. Total number of 416 courses was administered (median 6, range 1–9). The main toxicity was myelosuppresion; grade 3/4 neutropenia, thrombocytopenia and anemia occurred in 55%, 53% and

29% of pts, respectively. Non-hematologic side effects were mild. Out of 76 evaluable pts 6 (8%) achieved a complete response and 26 (34%) achieved a partial response, for an overall response rate of 42% (95% CI 31–53%). The median time to progression was 161 days, the median overall survival – 303 days and the one-year overall survival – 32%. QoL analysis showed an improvement of global QoL, physical activity and symptomatic release in 27%, 28% and 34% of pts, respectively. Release of specific symptoms: dyspnoe, chest pain and hemoptysis was achieved in 34%, 22% and 20% of pts, respectively. In conclusion: the combination of G and P, apart of its activity and acceptable toxicity, results in subjective benefit in advanced NSCLC.

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994 POSTER

P53 gene mutations are associated with poor prognosis in adenocarcinoma of the lung

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Mutation of P53 suppressor gene is the most frequent molecular alteration in NSCLC, but its clinical relevance is a matter of controversy. The aim of study was to determine the prognostic value of this abnormality in 151 NSCLC pts (92 from Poland and 59 from Spain) who underwent radical resection between 1986 and 1992. Major clinical characteristics were: 133 males and 18 females, median age 62 years (range 33–82), 97 squamous cell carcinoma, 46 adenocarcinoma and 8 large cell carcinoma. DNAs from paraffin-embedded tumor tissue samples were screened for mutations in exons 5–8 with the use of PCR/SSCP technique and positive samples were subsequently subjected to direct sequencing. Our previous report on this series showed poor prognosis associated with P53 null mutations (Oncogene 1997; 15: 2951). In the present analysis based on longer follow-up (median 5.1 years) and including more events (90 deaths out of a total of 151 cases) we confirmed negative prognostic impact of null mutations; median survival in pts with and without this abnormality was 10 and 42 months, respectively ($p = 0.027$; log rank). Additionally, in a group of 46 adenocarcinoma pts we noted a significantly shorter overall survival in subjects whose tumors carried P53 mutations (median survival in pts with and without mutation was 5 and 30 months, respectively; $p = 0.011$). The multivariate Cox analysis showed that in this tumor type stage of disease ($p = 0.024$, hazard ratio 1.58; 95% CI 1.06–2.36) and the presence of P53 mutation ($p = 0.026$, hazard ratio 2.75; 95% CI 1.11–5.91) were the only significant determinants of survival. These findings suggest independent prognostic value of P53 mutation in adenocarcinoma of the lung.

995 POSTER

Assessment of the new postsurgical pathological staging classification in NSCLC

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Precise staging of primary tumor and regional lymph nodes is of paramount importance in estimating prognosis and selecting a therapeutic strategy in NSCLC. The aim of this analysis was to assess the appropriateness of revised (1997) pTNM stage grouping in a series of 500 patients who underwent complete resection of NSCLC between Jan. 1986 and Dec. 1995. Study group included 399 males and 101 females; mean age 59 years (range: 33–78); 319 squamous cell carcinoma, 125 adenocarcinoma, 37 large cell carcinoma and 19 other types. Median survival and 5-year survival rate (5-SR) for the entire group were 35 months and 41%, respectively. The 5-SR in particular stages (after exclusion of 12 perioperative deaths) were as follows: IA (n = 35): 77%; IB (n = 179): 58%; IIA (n = 4): 50%; IIB (n = 101): 31%; IIIA (n = 123): 16%; IIIB (n = 19): 26%; IV (n = 8): 13%. There was a good distinction between newly split IA and IB (5-SR 77% and 58%, respectively; $p = 0.039$; Wilcoxon test) and between T3N0 and new stage IIIA (34% vs 16%, respectively: $p = 0.007$). No difference was found between T3N0 and T2N1, the categories constituting new stage IIB (5-SR 34% and 29%, respectively; $p = 0.51$). Within stage IIIA there is a striking difference between T3N2 and other TN constellations (5-SR 7% and 19%, respectively; $p = 0.011$). Relatively good results in stage IIIB and IV are probably due to high selection for surgery in these categories and exclusion of perioperative mortality. In new classification stage IIA is underrepresented (<1%). In conclusion: our results confirm the adequacy of the revised stage classification in establishing a prognostic hierarchy in operable NSCLC. T3N2 should be considered as a separate category in future stage groupings.

996 POSTER

Lack of prognostic significance of angiogenesis in non-small-cell lung carcinoma

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Purpose: Tumor angiogenesis plays a pivotal role in tumor growth, maintenance and metastasis. Our aim was to evaluate the prognostic value of tumor angiogenesis in 176 primary tumors from patients operated for non-small-cell lung carcinoma.

Methods: Tumor microvessels were stained by immunohistochemistry for CD34, and angiogenesis was estimated both by a modification of the method described by Weidner (hot spots) and by the use of a Chalkley grid. The vascular data were correlated to other known parameters: overall survival, sex, age, TNM-classification, grade and clinical stage.

Results: The median number of hot spot was 67 (range 27–278) in a counting area of 0.25 mm2, and the median average vascular score by the Chalkley grid was 7.0 (range 3.0–15.0). The counts estimated by the two methods were significantly correlated by Kendall's tau statistics ($P < 0.0001$), and the counts were reproducible. Our data demonstrated significantly prognostic value of stage ($P < 0.0001$), adenocarcinoma ($P = 0.002$), and age ($P = 0.01$). However, none of the estimates of vascular score revealed any prognostic value whatsoever.

Conclusion: In conclusion, our data do not support a significant prognostic role for tumor angiogenesis in patients diagnosed with non-small-cell lung carcinoma after long-term follow-up.

997 POSTER

Response of symptomatic brain metastases of small cell lung cancer (SCLC) to topotecan also after preceeding whole-brain radiation (WBI)

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Purpose: To evaluate the activity and toxicity of the new topoisomerase-1-inhibitor topotecan in patients with relapsed SCLC with symptomatic brain metastases.

Methods: Eiligible for this phase II study were patients with symptomatic brain metastases of recurrent SCLC after no more than 2 chemotherapy protocols or WBI. Topotecan was administered as a 30-minute intravenous infusion of 1.5 mg/m^2 for 5 consecutive days every 3 weeks.

Results: Fifteen patients were entered and treated with the total of 42 courses. Eight patients were pretreated with WBI. Systemic metastases were found in 12 patients. Response of the brain metastases was reached in 6 (40%) patients: complete response in 2 (13%) and partial response in 4 (27%) patients. Three of these patients were pretreated by WBI. Systemic responses paralleled tumor reduction in the CNS. Median duration of response was 75 days, median overall survival from first diagnosis was 501 days. No neurologic deterioration was observed during the chemotherapy. Toxicity was mainly hematologic with CTC grade 4 leukopenia and thrombopenia occurring in 12 (29%) and 18 (43%) of the courses, respectively.

Conclusion: Topotecan has a significant activity in pretreated patients with symptomatic brain metastases of SCLC. The schedule is well tolerated with myelotoxicity being the most common adverse event.

998 POSTER

Taxol and cisplatin (TP) versus etoposide cisplatin (EP) in advanced non-small cell lung cancer (NSCLC)

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Purpose: To assess, in a randomised phase II trial, the results obtained in advanced (st IIIB and IV) NSCLC pts with TP versus the standard EP regimen.