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.

Methods: From 9/96 to 2/99, 79 previously untreated pts received either TP (Taxol 200 mg/m^2, Cisplatin 80 mg/m^2 d1) or EP (Etoposide 100 mg/m^2 d 1–3, Cisplatin 80 mg/m^2 on d1) q3wks. St IIIB pts had 3 cycles (cyc) followed by RT at 60 Gy; st. IV up to 6 cyc (less if progressive disease).

Results: 84% males; age 56 [34–68]; WHO PS 0&1 in 45, 2 in 34 pts; histology (H): squamous 52, adeno 15, large cell 8, mixed 4 pts; AJCC st: IIIB 50, IV 29 pts; TP 32, EP 47 pts. **Toxicity** (tox): 256 cyc were given, with one toxic death in EP arm (renal failure). Gr. 4 haematological tox was rare (neutropenia 7, anaemia 1 cyc, in both arms). Gr. 1 neurological and cardiac tox occurred in 4 and 1 TP pts, respectively. **Activity:** 29 pts had an objective response (OR) to CT (= 37%, CI [26%–47%]), 4 CR, 25 PR. Response rate was influenced by the PS (0–1 vs 2: 49% vs 21%, $p < 0.01$) and weight loss ($\leq$5% vs $>$ 5%: 45% vs 17%, $p < 0.02$). Factors not significant for OR: protocol TP vs EP, stage, sex, age, H. **Survival** (S): at a median follow-up of 8 months (m) [1–23], median S is 7.5 m; 9 vs 7 m for st IIIB vs st IV pts ($p < 0.03$); 10 vs 6.5 m for CT responders vs refractory pts ($p < 0.01$). A trend existed in favour of TP (median S – TP vs EP: 9 vs 7 m, 1-year S 34% vs 14%), but not statistically significant. S was not influenced by sex, age, PS, weight loss or H. To date, 27 pts are alive and 52 have died: 49 pts disease progression, 1 trt complication, 2 other causes.

Conclusions: 1) TP and EP were equally active in advanced NSCLC pts (OR 38% vs 36%). 2) There was a trend towards improved S with TP. 3) Prognostic factors found: for response – PS and weight loss; for survival-stage and response to CT.

999 POSTER

A multicenter phase II trial with gemcitabine (GEM) and vinorelbine (VNR) in the treatment of non-small cell lung cancer (NSCLC) stage IIIB and IV

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Purpose: To evaluate the efficacy and safety of a combination with GEM and VNR in the first line treatment of advanced NSCLC.

Methods: Patients (pts) with NSCLC stage IIIB or IV received GEM 1000 mg/m^2 and VNR 30 mg/m^2 on days 1, 8, 15, every 4 weeks to a maximum of 8 courses. GEM was given over a 30-min infusion followed one hour later by VNR (15-min infusion). The doses of GEM and VNR were modified as follow: neutrophils $>$ 1.5/nl and platelets $>$ 100: no reduction, neutrophils 1.0–1.49/nl or platelets-75–99/nl: 50% dose reduction, neutrophils $<$ 1.0/nl or platelets $<$ 75/nl: delay.

Results: Between Dec 1997 and Nov 1998 70 pts with KPS 70–100% were enrolled. We can present preliminary data of 62 pts (study on going): 12.9% stage IIIB/87.1% stage IV; 48 male/14 female; mean age 58.6 (range 38–74). Histologic types: adenocarcinoma 40.3%, squamous cell carcinoma 27.4%, large cell carcinoma 24.2% and other classified NSCLC 8.1%. 50 pts were evaluable for response and 56 pts for toxicity. The overall response rate (ORR) was 46%. 1 CR (2%), 22 PR (44%), 13 SD (26%), 14 PD (28%). 174 cycles of chemotherapy were given. Toxicity (WHO): leukopenia G 3: 14.9% and G 4: 6.9%, thrombocytopenia G 3: 1.7% and G 4: 0.6%, anemia G 4: 1.7% of cycles. 3.6% of 56 pts presented G 2 and 5.4% G 3 peripheral neurotoxicity, 14.3% G 2/5.4% G 3 local phlebitis, 10.7% G3 infections, 5.4% G2/5.4% G3 reactions of skin, 3.6% G 3 vomitus/emesis, 5.4% G 3 pulmonary toxicity, 1.8% G 3/1.8% G 4 constipation, 5.4% G 2/5.4% G 3 mucositis, 3.6% G 3 increase of transaminases, 1.8% G 3 alopecia. 28 (16.1%) reductions of doses and 38 (21.8%) delays occurred in the administration of GEM and VNR.

Conclusions: These preliminary results suggest that the combination of GEM and VNR has major antitumor efficacy in advanced NSCLC with manageable toxicity. Although the sequence of drugs applied remains obscure, we believe that our sequence contributed to the comparatively high response rate. In summer 1999 we will start a multicenter randomized phase III study (GEM + VNR vs GEM + VNR + CDDP) in Germany to investigate the role of cisplatin. To avoid hematological toxicities GEM and VNR will be given on days 1 and 8 within 3-weeks cycles.

1000 POSTER

Raltitrexed ('Tomudex') and oxaliplatin: An active out-patient regimen in malignant mesothelioma

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Introduction: A previous Phase I study showed that a combination of raltitrexed ('Tomudex') and oxaliplatin appeared to yield some activity in both pre-treated and chemotherapy-naive mesothelioma patients (pts) [Fizazi et al, ASCO 1998]. The aim of this Phase II study was to further evaluate the activity of this combination in malignant mesothelioma. We present validated results from the first 23 pts.

Methods: Raltitrexed 3 mg/m[2] was given by a 15-min iv infusion followed 45-min later by oxaliplatin 130 mg/m[2] 2-h iv infusion repeated every 3 weeks.

Results: 50 pts (37 M/13 F) with a median age of 59 (range 43–74) yrs, and a WHO performance status of 0 (12 pts), 1 (27 pts) or 2 (11 pts) have been entered. 11 pts were pre-treated with platinum-based chemotherapy and 39 were chemotherapy naive. Among the 23 pts fully evaluable for safety, the following toxicities (NCI-CTC grade II and above) were recorded: grade II anaemia (3 pts), neutropenia (1 pt), vomiting (3 pts), nausea (2 pts), paresthesia (3 pts) and asthenia (12 pts), and grade III asthenia (2 pts), neutropenia (1 pt) and diarrhoea (1 pt). Response (WHO criteria) imaging evidence has been reviewed by an external panel. 21 pts are evaluable for efficacy (2 pts are ineligible due to the absence of measurable disease) and, of these, a partial response was seen in 6 pts (28.6% [95% CI 9.2–47.9]), stable disease (including 6 minor responses) in 11 pts (52.4%), and progressive disease in 4 pts (19%). Among the 16 evaluable chemotherapy-naive pts, 5 achieved partial response (31.3%), 8 had stable disease (50%) and 3 progressed (18.7%). In the pre-treated population, 1 partial response was seen in a cisplatin-refractory patient, 3 pts had stable disease and 1 pt progressed.

Conclusion: This preliminary activity/toxicity report shows that raltitrexed plus oxaliplatin has an acceptable tolerability profile and is active in malignant mesothelioma. Accrual is ongoing.

'Tomudex' is a trade mark, the property of Zeneca Ltd.

1001 POSTER

Cisplatin – Paclitaxel – Topotecan (CPT) weekly administration in chemo-naive or pretreated extensive disease small cell lung cancer (ED-SCLC). A SICOG Phase II study

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Purpose: To define the antitumor activity of the CPT weekly administration with G-CSF support in chemo-naive or pretreated SCLC pts with extensive disease.

Methods: Pretreated or chemo-naive patients with ED-SCLC received Cisplatin 40 mg/m^2, Paclitaxel 85 mg/m^2 and Topotecan 2.25 mg/m^2 weekly, with filgrastim (5 μgr/kg d 3–5) support. A minimum of 6 weekly cycles were delivered. In presence of major response additional 6 cycles were given.

Results: To date, 26 ED-SCLC patients (20 chemonaive, 6 pretreated) have been treated, for a total of 158 cycles delivered. The treatment was generally well tolerated. Grade 4 neutropenia and thrombocytopenia occurred in 3 and 1 pts, respectively. Anemia was more frequent and 3 blood transfusions were required. Severe diarrhoea, parhestesias and fatigue occurred 6, 2 and 8 pts, respectively. At the present analysis 18 chemo-naive and 5 pretreated pts are evaluable for response. 3 CRs and 10 PRs have been recorded in chemo-naive pts for a 72% ORR. One complete and 2 partial responses have occurred in the 5 evaluable pretreated pts. At a 7 (1–16)-month median follow-up only 3 deaths have occurred.

Conclusions: The weekly CPT combination with G-CSF support represents a well tolerated therapeutical approach either in chemo-naive or pretreated ED-SCLC pts. The activity rate in chemo-naive pts. seems at least similar to that achievable with the standard front-line approaches. The study continues until the planned final sample size of 53 pts.