Patients and Methods: From December 1990 to August 1994, nine patients (5 male, 4 female), mean age 58.5 years, with histologically verified bronchial cancer were treated. Two patients had early (T1) disease, whereas the other 7 patients had recurrent disease or residual tumour following primary therapy by surgery or radiotherapy. Histology was NSCLC in all cases (5 squamous cell cancer, 3 adenocarcinoma, 1 alveolar cell cancer). Laser treatment was performed with a continuous wave Argon dye laser using 532 nm (2W, with 200 J/ccm dose) by endobronchial access under general anaesthesia.

Results: The overall response rate was 8/9. One patient did not show any effect of the tumour following PDT. In two cases the response was complete (CR) following PDT, in one additional patient CR was achieved following additional radiotherapy. Seven patients had bronchial obstruction due to tumour, in 5 cases there was a marked >50% reduction in the stenosis as evaluated by bronchoscopy. Treatment tolerance was excellent, with only minor distress caused by hosptalisation for light protection. Weight increase and increase in Karnofsky performance was noted in 4/9 patients. Two patients have died due to local tumour progression, in 4 patients death was due to distant metastases. Three patients have remained well with no evidence of disease.

Conclusion: PDT offers potential cure for early cancers of the lung and is of value as palliative measure in advanced disease. The advantage of PDT is its possible use when surgery and/or radiotherapy are not considered treatment options. Development of new sensitisers will facilitate the use of PDT and will decrease side effects and discomfort due to hospitalisation.

1020 PUBLICATION

Value of CYFRA 21-1 as determinant of survival and predictor of disease course in lung cancer patients

P. Barradas[1], A. Costa[1], M. Cristovao[1], A.L. Fragoso[1], P. Alves[1], M.J. Melo[1]. [1]*Hospital de Pulido Valente, Oncology Division, Department of Pulmonary Medicine, Lisbon, Portugal*

Purpose: To evaluate diagnostic and prognostic value of CYFRA 21-1 and its interest as predictor of lung cancer course.

Methods: CYFRA 21-1 serum levels were measured in 532 pts with lung cancer and 160 pts with a variety of benign diseases. In 257 out of 408 pts submitted to chemotherapy (CT) serum measurements were also performed after 3 cycles of treatment. In 74 NSCLC pts CYFRA 21-1 were monitored every 3 months.

Results: Median values of CYFRA 21-1 in 160 pts with benign lung diseases (1.7 ng/ml IR-1.0–2.3) were significantly lower than in lung cancer patients (4.3 ng/ml IR-1.9–9.5 $p < 0.001$). Using cut-off value of 3.3 ng/ml (90% specificity for benign lung disease) overall sensitivity for lung cancer was 57.2% (NSCLC-62.0%; SCC-77.5%). Univariate survival analysis showed that CYFRA 21-1 above 3.3 ng/ml was strongly related with a poor median survival ($p < 0.00001$). Cox's multivariate analysis indicated that CYFRA 21-1 was a strong independent prognostic factor for survival. Initial CYFRA 21-1 values didn't correlate with response to CT but changes at 3rd cycle were significantly related to response ($p < 0.001$). Changes in CYFRA 21-1 values over time (remission = decrease of at least 50% of the initial CYFRA 21-1 values; progression = increase of 50% of the initial CYFRA 21-1 values; stabilisation = decrease below 50% or increase below 50%) were closely related with clinic/radiological assessment (diagnostic efficacy: 86.7%). In 47.3% of pts significant increases in CYFRA 21-1 preceded clinic or radiological evidence of disease's progression.

Conclusion: CYFRA 21-1 is a strong prognostic factor for survival and very useful to monitor therapy and to detect early changes in disease's course.

1021 PUBLICATION

Combination chemotherapy with Cisplatin (CDDP) and Adriamycin (ADM) plus immunotherapy with interferon (IFN) alfa-2b in malignant pleural mesothelioma (MPM): Results of a phase II trial of the Italian Group on Rare Tumors (GITR) and Italian Lung Cancer Task Force (FONICAP)

H. Soto Parra[1], S. Bretti[1], A. Ardizzoni[2], L. Tixi[2], F. Latteri[1], A. Gravina[2], R. Lionetto[1], P. Bruzzi[1], A. Santoro[1], R. Rosso[2]. [1]*Italian Group on Rare Tumors (GITR), Milan;* [2]*Italian Lung Cancer Task Force (FONICAP), Italy*

Background: MPM is a rare tumor for which no standard treatment is available. Anthracyclines and CDDP, as well as IFN, have been reported to have some activity in this disease. In addition, pre-clinical studies have shown synergism between IFN and chemotherapy in mesothelioma cell-lines.

Methods: from 12/95, we conducted a phase II trial in previously untreated patients to assess the toxicity and antitumor activity of a chemo-immunotherapy regimen including CDDP 60 mg/sqm i.v. day 1 plus ADM 60 mg/sqm i.v. day 1, recycled every 3–4 weeks and IFNalfa-2b, 3 MIU i.m. 3 times a week for a maximun of 8 courses or until progression. Inclusion criteria were histological diagnosis of MPM and measurable disease defined by CT scan or MRI. Tumor assessment was performed every 3 cycles with CT or MRI. Based on a two-stage Simon's design, a target accrual of 35 pts was planned.

Patient characteristics: 35 pts were registered with the following characteristics: male 26 pts; median age 58 yrs (40–71); ECOG PS 0 in 8 pts, 1 in 25, 2 in 2; epithelial subtype in 18 pts; 5 pts were classified as stage I, 5 as stage II, 12 as stage III and 10 as stage IV.

Results: two pts were ineligible, 2 had insufficient data and 3 are still ongoing. 29 pts were assessable for toxicity and 32 for response on an intention to treat basis. Seven pts had a partial response for an overall response rate of 22% (95% CI, 10%–40%); 35% had stable disease. The median response duration was 8.5 months (range, 2+–12+). The median survival was 11.2 months. 6 out of 7 responding pts are still alive.

Toxicity: 113 cycles of CDDP + ADM plus IFNalfa-2b were given, with a median of four cycles per patient (range, 1–8). Main toxicity was grade III–IV myelosupression: leukopenia in 75% of pts, thrombocytopenia in 21% and anemia in 29%. Other grade 3/4; toxicities were fatigue in 31%, emesis in 24%, myalgias in 7% and renal failure in 3%. Toxicity leaded to treatment withdrawal in 9 pts.

Conclusion: This combined chemo-immunotherapy is active in MPM but the high toxicity observed, particularly myelosuppression, may limit its application.

1022 PUBLICATION

Endothelial cells and angiogenesis intensity in lung cancer

L. Chyczewski[1], M. Juczewska[2], J. Niklinski[3], W. Niklinska[4], E. Chyczewska[5], W. Naumnik[5]. [1]*Departents of: Pathomorphology,* [2]*Oncology;* [3]*Thoracic Surgery;* [4]*Histology;* [5]*Pneumonology, Bialystok Medical Academy, Bialystok, Poland*

Neovascularization in compliance with histological type, differentiation and pathological stage of cancer was evaluated in 65 tumors taken from patients operated for lung cancer. Angiogenic objects (microvessels and single endothelial cells) were highlighted by immunohistochemical method for von Willebrand factor. Angiogenic objects count per 1 mm^2 in each section was determined in "hot spot" found at the margin of tumors. The own scale of angiogenesis intensity was used: I°-0–200, II°-201–400, III°->400 angiogenic objects/mm^2. Majority (57%) of examined cases were found in II° group. The results of studies on single EC number/mm^2 in different histological types of cancers were following: 158.01 ± 119.37 in SqCC, 191.97 ± 67.6 in ADC, 219.17 ± 132.57 in LCC, 231.16 ± 45.01 in SCC, 269.69 ± 173.67 in combined cancers. The differences between EC counts in the groups with different histological type of lung cancer were statistically significant in the pairs: squamous cell versus small cell ($p = 0.0247$) and adenocarcinoma versus small cell ($p = 0.0380$). The correlation between EC count in "hot spot" and grade of tumor differentiation was statistically significant for G1 group versus G4 ($p = 0.0008$) and G1 versus G2 ($p = 0.0380$).

These results suggest the role of EC in angiogenesis in lung cancer is greater that it had been expected before.

1023 PUBLICATION

Paclitaxel/epirubicin/etoposide in patients with extensive-disease small-cell lung cancer (SCLC)

E. Baldini[1], A. Chella[2], A. Del Freo[1], F. Gragnani[2], C.A. Angeletti[2], P.F. Conte[1]. [1]*Osp. S. Chiara, U.O. Oncologia Medica, Pisa;* [2]*Osp. S. Chiara, U.O. Chirurgia Toracica, Pisa, Italy*

Paclitaxel (P) and Epirubicin (EpiDx) shows high antitumor activity against SCLC while Etoposide (E) is the most active single-agent in this disease. We performed a dose escalation study in order to identify a combination regimen in which each of the above mentioned drugs is administrered at its optimal dose. The starting doses were: P 155 mg/sqm (3-hour infusion) day 1, EpiDx 60 mg/sqm (bolus injection immediately before P) day 1, E 100 mg/sqm (i.v.) days 1–3; a maximum of 6 courses were repeated every 3 weeks. The dose of EpiDx was escalated by 15 mg/sqm in consecutive triplets of patients (pts) until 90 mg/sqm (optimal dose as single-agent -Basthold JCO 1996-). If Dose-Limiting Toxicity (DLT) was not met, P was escalated until 175 mg/sqm (optimal dose as single-agent -Nabholtz JCO 1996- -) in subsequent triplets of pts. E was administered at the fixed dose of 100 mg/sqm days 1–3. No intrapatient escalation was allowed.

DLTs were defined as follows: an absolute neutrophil count (ANC) < 500/ul for >7 days or <100/ul for 3 days; febrile neutropenia; any grade ≥ 3 (WHO) non-hematologic toxicity. Ventricular ejection fraction (LVEF) was evaluated by bidimensional ecocardiography (or MUGA scan) at entry and at the end of treatment. Twelve untreated pts with extensive-disease (ED) SCLC entered the study and were evaluable for toxicity. Median age 65 (range 61–70), median ECOG PS = 0 (range 0–1); six pts (50%) had brain metastases and 3 (25%) presented bone marrow involvement. Hematologic toxicities (WHO) are summarized below:

EpiDx	P	n. Pts	n. courses	ANC G4 (%)
60	155	3	18	/
75	155	3	18	/
90	155	3	18	11
90	175	3	11	27

No episode of febrile neutropenia was observed; only one pt with bone marrow involvement experienced grade 3 anemia and thrombocytopenia after the fifth course of CT. Baseline median EF was 63.3% (range 57–70%) and no significant modification was observed at the end of treatment. Even if activity was not the main end-point of the present study, responses were assessed every 3 courses: six out of 12 pts showed a complete response (CR) and 6 pts a partial response (>75%). Pts with celebral metastases received whole brain irradiation (30–36 Gy) concomitantly with chemotherapy courses and obtained a CR. In conclusion, the combination of P, EpiDx, E at optimal doses is feasible and its toxicity profile compares favourably with other three-drug-regimens commonly used. The mild and easy-to-manage hematologic toxicity reported make it possible for this regimen to be safely integrated with radiotherapy. In addition, this triplet shows promising antitumor activity. A multicenter phase II study is in progress in order to better define the antitumor activity of the combination.

1024 PUBLICATION

Paclitaxel, gemcitabin, and cisplatin in non-resectable non-small cell lung cancer (NSCLC)

J.B. Sørensen[1], L.E. Stenbygaard[2], H.H. Hansen[1], K. Østerlind[2].
[1]*Department of Oncology, Finsen Centre, National University Hospital;*
[2]*Department of Oncology, Herlev Hospital, Copenhagen, Denmark*

Purpose: To evaluate the activity of a new 3-drug chemotherapy regimen in a phase II study in patients (pts) with NSCLC.

Methods: Inclusion criteria were: Non-resectable NSCLC, no prior chemotherapy, no brain metastases, performance status 2 or better, normal organ function, and measurable disease. Doses and schedule were: Gemcitabin 1000 mg/m^2 i.v. day and 8, Paclitaxel 180 mg/m^2 i.v. day 1, and Cisplatin 100 mg/m^2 i.v. day 1, every weeks.

Results: Pretreatment characteristics for 29 included pts were: Female/male ratio 15/14; median age 58 years (range 42–68); stage IIIA 14%, IIIB 48%, IV 38%; performance status 0 44%, 1 28%, 2 28%; adenocarcinoma 62%, squamous cell 24%, large cell 3%, adenosquamous 7%, unclassified NSCLC 3%. 27 pts were evaluable for toxicity, which was mainly hematological with WHO grade III or IV neutropenia in 92% of pts, and thrombocytopenia in 63%. Non-hematologic grade WHO grade III toxicity were: nausea/vomiting 41%, neurotoxicity 7%, nephrotoxicity 26%, while none had grade IV non-hematological toxicity. There were 12 episodes of febril neutropenia in 11 pts with 1 toxic death, and 4 bleeding episodes in 4 pts. Among 22 pts evaluable for response there were 12 partial, and 1 complete response (59%, 95% confidence limits 36–79%). Median time to response was 12 weeks and median response duration 21 weeks (range 10+–50+ weeks).

Conclusions: This new 3-drug regimen in NSCLC seems promising, with a substantial number of long lasting responses. Toxicity was generally manageable, though pronounced, and modifications might improve the feasibility. The study is ongoing to 40 evaluable patients.

1025 PUBLICATION

Gemcitabine monotherapy in elderly advanced NSCLC patients

G. Altavilla[1], V. Adamo[1], B. Buemi[1], G. Marabello[1], A. Bene[2], G. Lupo[1], M. Chiarenza[1], G. Bellocco[1]. [1]*Inst. of Clinical Oncology, Univesrity of Messina, Messina;* [2]*Sez. dec. IST Genova, University of Messina, Messina, Italy*

In phase II trials Gemcitabine (Gem) showed to be an active agent in NSCLC, producing a clinical benefit often higher than response rate.

We assessed the impact of Gem treatment in obtaining therapeutic response and better quality of life in 21 untreated ederly patients (aged >70 years) with NSCLC, enrolled from 1/87 to 8/98. The main characteristics of patients were: M/F 18/3; median age 74 years; stage III B 7, IV 14. The schedule was: Gem 1250 mg/sm i.v. days 1–8 q. 21 days. Response and toxicity have been analyzed according WHO criteria. Clinical benefit has been evaluated by patient visual analogue symptoms score, the ECOG Performance Status and weight.

All patients are evaluable: we found 7 PR (33%), 5 SD (24%) and 9 PD. WHO grade 2 leukopenia (in 4 pts) and trombocytopenia (grade 3 in 1 pt. and grade 2 in two pts.) have been the main toxic effects. A clinical benefit has been demonstrated in all 12 patients with PR or SD and in 3 patients with PD.

These data confirm that Gemcitabine monotherapy is a well tollerated and active therapeutic approach in ederly NSCLC patients and stress its role in determining a clinical benefit.

1026 PUBLICATION

Combination of docetaxel and gemcitabine in the treatment of advanced non-small cell lung cancer (NSCLC)

N.V. Jensen[1,2], O. Hansen[1], C. Rose[1]. [1]*Odense University Hospital, Department of Oncology, Odense;* [2]*University of Southern Denmark, Clinical Pharmacology, Odense, Denmark*

Docetaxel and gemcitabine are two of the most active single agents in the treatment of non-small cell lung cancer (NSCLC). The purpose of the study was to evaluate the tolerance and efficacy of the combination containing these two drugs in the treatment of patients with advanced NSCLC.

Twenty-three patients with NSCLC stage IIIb or IV, median age 60 years (range 36–69) entered the study till now. The male/female ratio was 16/7. Six of the patients were treated previously with first-line chemotherapy including cisplatin or carboplatin. In the present protocol chemotherapy was administered in a three-week treatment cycle in which docetaxel was given on day 1 and gemcitabine on days 1 and 8 with a maximum of 6 cycles per patient. The patients were treated at three dose levels: 1): docetaxel 75 mg/m^2 and gemcitabine 800 mg/m^2 (including only the pre-treated patients), 2): docetaxel 80 mg/m^2 and gemcitabine 800 mg/m^2 and 3): docetaxel 80 mg/m^2 and gemcitabine 900 mg/m^2. Six patients entered at dose level 1, twelve at dose level 2 and five at dose level 3. Neutropenia NCI-grade 3 or 4 was observed at all dose levels (at dose level 3 in two of five patients). Diarrhoea NCI-grade 3 was seen in four patients (three at dose level 1 and one at dose level 3). Diarrhoea grade 2 was seen in five patients at dose level 2.

Maximal tolerated dose has been reached at dose level 3 with three of five patients experiencing grade 3 or 4 side effects (neutropenia (2) and diarrhoea (1)). Of twenty-two patients evaluable for response partial response was achieved in nine (39%). The recommended dose for phase II-trials is docetaxel 80 mg/m^2 (day 1) and gemcitabine 800 mg/m^2 (day 1 and 8) in a three-week cycle. The study is ongoing including patients at dose level 2 and evaluating the patients' self-reported quality of life.

1027 PUBLICATION

A phase II study of paclitaxel (P) and carboplatin (C) as second-line treatment in patients (PTS) with small-cell lung cancer (SCLC)

S. Agelaki, M. Agelidou, G. Blazogiannakis, X. Tsiafaki, Th. Palamidas, Ch. Kouroussis, S. Kakolyris, Ch. Malliotakis, G. Samonis, V. Georgoulias. [1]*The Greek Lung Cancer Cooperative Group, United Kingdom*

Background: There is no standard treatment for pts with SCLC relapsing after first-line therapy. Both P and C have demonstrated activity in this setting and there is evidence of synergism between these agents. We conducted a phase II study to evaluate the efficacy and toxicity of P and C combination as second-line treatment in patients with SCLC. Patients and treatment: Twenty-one SCLC pts (18 male, 3 female) progressing after first line chemotherapy were enrolled. Front-line treatment included cis-platin and etoposide (17 pts) and cyclophosphamide, adriamycin and vincristine (4 pts). All but 3 pts (85%) had disease progression or relapse within 3 months after front line therapy (refractory disease). P (200 mg/m^2) was administered on day 1 as 3 hr iv infusion, and C at 6 AUC (Calvert formula) iv on day 2, cycles repeated every 4 weeks. rhGCSF was administered prophylactically in case of previous grade 3/4 neutropenia. The median age was 63 years (range 43–77); PS (WHO) was 0 (6 pts), 1 (13 pts) and 2 (3 pts).

Results: Eighteen pts were evaluable for response and 21 for toxicity. Grade 3/4 neutropenia without fever was observed in 6 (28%) pts. Thirteen pts (61%) required GCSF. Two pts (10%) developed non-neutropenic fever.