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)

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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

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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)

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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)

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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.

Grade 3/4 anemia occurred in 1 pt (5%) and grade 3 thrombocytopenia in 3 pts (14%). Non hematological toxicity was mild; 3 pts (14%) developed grade 3 neuropathy and 7 pts (34%) grade 2/3 asthenia. Mild hypersensitivity reactions occurred in 2 pts (10%). A total of 62 cycles were administered (median number: 3 cycles/pt). The median administered dose intensity was 100% of the planned dose for P and 85% for C. Three pts (17%) achieved partial response, 5 pts (28%) stable disease and 10 pts (55%) progressive disease Two of the responding patients had refractory disease and responses lasted for 4.5 months (2 pts) and 2.5 months (1 pt). The median TTP was 5.5 months (range: 3–10) and the median overall survival was 7 months (range: 1–14.5).

Conclusion: The P + C combination is a well tolerated and active regimen as second line therapy in patients with SCLC.

1028 PUBLICATION

Phase II multi-institutional study of Irinotecan (CPT-11) and Cisplatin (CDDP) on a three-week schedule in patients with advanced non-small cell lung cancer (NSCLC)

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Introduction: Irinotecan (CPT-11) is a promising new drug in non-small-cell lung cancer (NSCLC). The combination of CPT-11 and CDDP is being developed with the aim of having a regimen with potential effectiveness for NSCLC and other solid tumours as well. The optimal schedule of the combination is not established.

Patients and Methods: Patients eligible had histologically confirmed NSCLC, measurable disease, stage IV or IIIB non suitable for radiotherapy, age = <71 years, ECOG performance status = <2. Patients previously treated with chemotherapy for advanced disease or with symptomatic brain metastases were not eligible. CPT-11 200 mg/m^2, given as a 60 minute i.v infusion, was immediately followed by CDDP 80 mg/m^2 i.v. on day 1. Cycles were repeated every 21 days. In case of delayed diarrhoea immediate therapy with loperamide was started. Prophylactic use of haematopoyetic growth factors was not permitted.

Preliminary Results: From July 98 to February 99, 48 patients have been recruited. 43 are currently evaluable for toxicity and 32 for efficacy. 125 cycles have been administrated (median: 3, range: 1–8). Median age: 59 (43–71) years; M/F: 37/6. 18% IIIB, 82% IV.

Histology: 33% squamous cell carcinoma, 37% adenocarcinoma, 22% large cell carcinoma, 8% non differentiated carcinoma. Main toxicities (% patients) were neutropaenia (NCI grade 4) 11.6%, diarrhoea (NCI grade 4) 9.3%, nausea and vomiting (NCI grade 3) 16.2%, asthenia (NCI grade 3) 8.1%.

32 patients are available for efficacy after 3 cycles. 13/32 achieved partial response, 11/32 stable disease and 8/32 progressed. Updated results will be presented.

Conclusion: Preliminary data suggest that irinotecan and cisplatin on this particular schedule have a manageable toxicity profile and that this combination is fairly active in NSCLC.

1029 PUBLICATION

Gemcitabine-cisplatin-vinorelbine phase II trial in stage III non small cell lung cancer

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Purpose: To assess efficacy and toxicity of Gemcitabine (GZ)-Cisplatin (CP)-Vinorelbine (VN) in stage II non small cell lung cancer (NSCLC).

Methods: From Jan/98 to Jan/99 46 patients (pts) were enrolled, 43 were male and 3 female, median age 63.5 years (42–75), ECOG PS 0/1/2 was 10/35/1, stage IIIA/IIIB were 11/35, and histology squamous/adenocarcinoma/large cell was 32/9/5. It was required to have histologically proven NSCLC subsidiary of radical management. Treatment was GZ 1000 mg/m^2 on days 1 and 8, CP 100 mg/m^2 on day 1 and VN 25 mg/m^2 on days 1 and 8, every 21 days.

Results: To Feb/99 37 pts were evaluable for response and all for toxicity. Overall response rate was 62% (95% CI: 47–77%) with 2 clinical CR (5%) and 21 PR (57%), 12 SD (33%) and 2 PD (5%). After treatment 7 pts were sent to surgery and 27 to radiotherapy. Even with a short follow-up, 7 pts are death (2 due to toxicity) and 39 are alive. A median of 3 cycles per pts (1–6) were administered. In % over total sessions CTC grade 3 toxicity was anemia in 2.2%, neutropenia in 14%, thrombocytopenia in 5.1%, nausea in 2.9%, vomiting in 7.4%, creatinine in 1.4%, pulmonary edema and stomatitis in 0.7% each one. Grade 4 toxicity was neutropenia in 13.3% (6 febrile), thrombocytopenia and vomiting in 1.4% each one and dyspnea in 0.7%. Moderate and severe fatigue were reported in 11 and 6 pts. 16 hospitalizations and 2 toxic deaths were observed, and 3 pts left treatment due toxicity.

Conclusion: Although results toxic, these findings suggest that this regimen is very active in locally advanced NSCLC.

1030 PUBLICATION

Blood cell mitochondrial DNA (mtDNA) damage related to treatment in small cell lung cancer (SCLC) patients

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Purpose: Evidence of accumulation of the carcinogen agents in the mitochondria have been reported. To explore *in vivo* the effect of exogen agents, like chemotherapy (CT) or radiotherapy (RT) on mtDNA, we undertook the present study in SCLC patients.

Methods: 19 patients with SCLC (limited disease) were studied. All patients underwent the same treatment, based on four CT courses of carboplatin and oral etoposide, and chest RT. Blood samples were taken before and inmediatly after CT and every 12 weeks during the patients follow-up. Variations of three mtDNA mutations (mutations in tRNA genes of mtDNA) were detected by mutation specific PCR and assess them by a semiquantitative method, in mtDNA of blood cells; the ratio between mtDNA and nuclear DNA was also analyzed by the same semiquantitative method.

Results: The higher ratio of each mutation studied was observed inmediatly after the CT, decreasing to basal values during RT treatment and post-treatment visits. The top deviation of mtDNA with mutations, respect to basal values was between 3-fold to 80-fold. The correlation between ratio of mtDNA mutations and the total mtDNA showed that a low ratio of mutations correlates to increased mtDNA and viceversa.

Conclusion: Mitochondrial DNA of blood cells is damaged during CT administration and this injury is reverted after CT treatment. The amount of mtDNA increases with a low ratio of mtDNA mutations, and clearly decreases when a very high ratio of mtDNA mutations are present.

1031 PUBLICATION

A multi-centre phase II trial of gemcitabine (GEM) and vinorelbine (VRL) in patients (PTS) with stage III–IV non small cell lung cancer (NSCLC)

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Purpose: A multi-centre phase II study was conducted to evaluate the efficacy and toxicity of VRL plus GEM in pts with stage IIIb or IV NSCLC.

Patients and Methods: From March 1998 to September 1998, 40 pts were enrolled on study. VRL 20 mg/m^2 was given as a 10 minutes I.V., followed by a 30 minutes I.V. of GEM 800 mg/m^2 on days 1, 8, and 15 of each 28-day cycle.

Results: Twenty-two (55%) pts were stage IV and 7 IIIB (17.5%). The majority of pts were male (80%). Median age was 68 (range 39 to 84). Two pts achieved a complete response, and 27 pts achieved a partial response: overall response rate of 72.5%. (95% CI, 58.7%–86.3%). Median survival was 12 months. Significant (WHO grade 3/4) toxicities were myelosuppression, which included leucopenia (47.5% of pts), anemia (17.5% of pts), and thrombocytopenia (12.5% of pts). However, febrile neutropenia occurred only in 3 pts and accounted for one treatment-related death. Chronic fatigue syndrome, or flu-like syndrome, occurred in 17 pts and the symptoms recovered spontaneously one to two days after injections in 10 pts. Another 7 pts needed dose reduction to relieve symptoms. Interstitial pneumonitis occurred in 6 pts and recovered after steroid treatment. No patient experienced grade 3 or 4 nausea/vomiting.

Conclusion: The combination of VRL and GEM in advanced NSCLC is a highly active non-cisplatin containing regimen with acceptable toxicity profile.