1015 PUBLICATION

Cisplatin – gemcitabine – paclitaxel (PGT) in the treatment of advanced non-small-cell lung cancer (NSCLC). A southern Italy cooperative oncology group (SICOG) phase II study

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Purpose: To define the antitumor activity of the PGT combination in chemo-naive NSCLC pts

Patients and Methods: Patients with locally advanced or metastatic NSCLC were considered eligible if they had age ≤ 70 years and ECOG PS 0–2. They received P 50 mg/m^2, T 125 mg/m^2 and G 1,000 mg/m^2 d 1 & 8 q 3 wk.

Results: Since April 1907, 39 patients with stage IIIB (13) or IV (26) disease were enrolled for a total of 135 cycles delivered. ECOG PS was 0–1/2 in 31/8 patients. 38/39 pts were evaluable for response on an intent to treat basis. 2 CRs and 24 PRs have been recorded for a 68% [95% C.I. = 51–82] ORR. Major responses were 10/13 (77%) in IIIB and 16/25 (64%) in stage IV pts. The QoL score improved in 27/38 (71%) pts. At a 7 (range; 1–17)-month median follow-up the MST has not yet been reached, with a 1-year projected survival of 70%. Toxicity was generally manageable. Grade 4 neutropenia and thrombocytopenia were observed in 9 (23%) and 3 (8%) pts, and in 6 cases a packed red blood cell transfusion was required. Severe nonhematological toxicity occurred in 8 pts.

Conclusions: The PGT combination yields very high clinical response and QoL improvement rates in chemo-naive advanced NSCLC pts at a price of a manageable toxicity. A large phase III trial comparing this new regimen to standard combinations is underway.

1016 PUBLICATION

A phase II study of docetaxel (D) and gemcitabine (G) as second-line treatment in patients (pts) with advanced non-small cell lung cancer (NSCLC)

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Background: D and G have demonstrated single agent activity in both chemo-naive and previously treated pts with advanced NSCLC. They share different mechanisms of action. We conducted a phase II trial to evaluable the efficacy and tolerance of the combination as second line treatment in pts with advanced NSCLC. Patients and treatment: Twenty-nine pts with NSCLC (27 male, 2 female) who had progressed or failed first-line chemotherapy were enrolled. Prior chemotherapy was platimum-based with (n = 7) or without (n = 20) docetaxel and docetaxel-vinorelbine (n = 2). Patients received gemcitabine (900 mg/m^2 iv days 1 and 8) and docetaxel (100 mg/m^2 iv; day 8) every 3 weeks. G-CSF (5 ìg/kg, sc) was administered on days 9–18 prophylactically in case of previous grade 3/4 neutropenia. The median age was 63 years (range 27–74); PS (WHO) was 0 (7 pts), 1 (12 pts) and 2 (10 pts). Eight (28%) pts had stage IIIB and 21 (72%) had stage IV disease. Median number of disease sites per pt was 2 (range 1–3).

Results: Twenty-eight pts were evaluable for response and 29 for toxicity. Five (18%, 95% CI: 3.67%–32.04%) pts achieved partial response; 10 (36%) pts had stable disease and 13 (46%) progressed. After a median follow up of 6 months (range 1–19), the median duration of response was 5 months (range 1.5–8), the median TTP 11 months (range 3–16) and the median survival 7 months (range 1–19). The one-year survival rate was 20%. A total of 112 cycles were administered (median 3 cycles/pt). The median administered dose intensity was 100% of the planned dose for both drugs. Ten cycles (9%) were delayed due to toxicity. Neutropenia grade 3/4 occurred in 4 (14%) pts. Two (7%) pts experienced febrile neutropenia. There were no toxic deaths. G-CSF was required in 98 of 112 cycles (87%). Grade 2/3 anemia was observed in 15 (51%) pts, grade 2/3 asthenia in 14 (48) pts and grade 2 neurotoxicity in 3 (10%). Other toxicities were mild.

Conclusions: The D + G combination has tolerable toxicity and modest activity in terms of tumor growth control rate (PR + SD) as salvage treatment in advanced NSCLC.

1017 PUBLICATION

Phase II study of Docetaxel and Cisplatin in a circadian timing as first line chemotherapy (CT) in advanced non small cell lung cancer (NSCLC)

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Introduction: The combination of Docetaxel and Cisplatin used in a time unspecified fashion as first line CT in NSCLC produced 21–45% resonses with a median survival time of 8–12 month. Animal data showed improved efficacy and reduced toxicity if both agents were given in a circadian timing.

Methods: Based on these data the combination of Docetaxel and Cisplatin was investigated in the following time specified fashion: Docetaxel 75 mg/m" i.v. over 1 hour at 9 a.m. followed 7 hours later (4 p.m.) by 75 mg/m" Cisplatin i.v. over 30 minutes together with i.v. hydration. Cycles were repeated every 3 weeks. Steroids were given before and after Docetaxel. Patient characteristics: 63 pts. have received 240 cycles. 63 pts. are evaluable for toxicity and 56 pts. are evaluable for tumor response. M/F ratio: 49/14, median age 64 (43–75) years, median WHO performance status 1 (0–2).

Results: Neutropenia NCI-CTC grade 4 occurred in 10% of pts. and grade 3/4 in 19% of pts. Other toxicities of NCI-CTC grade 3/4 (platelets, anemia, diarrhea, stomatitis and vomiting) occurred in <5% of pts. No other toxicities of grade 3/4 were observed.

Response: In 56 pts. 27 (48%) PR [95% Confidence interval 35–62%], confirmed by CT-Scan, were achieved.

Conclusion: Present results indicate that Docetaxel/Cisplatin, given in a circadian timing, produces comparable response rates but significantly less NCI-CTC grade 4 and grade 3/4 Neutropenia than this combination in similar dosages in a time unspecified fashion does.

1018 PUBLICATION

Preoperative treatment with cisplatin-gemcitabine in locally advanced nsclc: Survival, toxicity and salvage surgery

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Purpose: To assess efficacy, toxicity and salvage surgery in patients with unresectable locally-advanced NSCLC treated with Cisplatin-Gemcitabine.

Methods: Between September-97 and October-98, 24 patients with unresectable NSCLC were included. Patients with pleural effussion and superior vena cava syndrome were excluded. Mean age: 55.5 years (43–69); 23 males and 1 female. Histology: 11 squamous cell, 10 adenocarcinoma and 3 undifferentiated carcinoma. Stages: 17 IIIA (clinical N2) and 7 IIIB. Treatment schedule: Cisplatin 100 mg/m^2 day 1 and Gemcitabine 1200 mg/m^2 days 1 and 8, every 21 days, to a maximum of 6 cycles, in an out-patient setting. Surgical salvage was evaluated after 3rd and 6th cycles with CT scan.

Results: 117 cycles were administered; mean: 4.8 (1–6). Hematological toxicity: neutropenia III, 3 episodes (ep) and anemia III, 1 ep. Extra-hematological toxicity: fatigue III, 10 ep. emesis III, 4 ep. and emesis IV, 1 ep. There was 1 toxic death because of pancytopenia. Overall response rate: 65%; 14 partial response (61%) and 1 complete response (4%). Stable disease, 3 (13%) and progressive disease, 5 (22%). Salvage surgery was performed in 7 patients (30%), with 5 pathologic partial response and 2 pathologic complete response. In 3 patients exploratory thoracotomy, without resection due to vena cava infiltration. Of the 7 patients resected, 4 are free of disease after 20.5, 13, 12.5 and 7 months. Median survival has not been reached. Actuarial survival at 18 months is 75%.

Conclusions: Cisplatin-Gemcitabine is an effective scheme of chemotherapy with high response rate, being possible salvage surgery. Toxicity is mild and manageable. Initial results are encouraging, but long term follow up will allow the impact of this aproach on overall survival.

1019 PUBLICATION

Photodynamic therapy in bronchial carcinoma

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Purpose: Retrospective evaluation of patients with bronchial carcinoma treated by photodynamic therapy (PDT).

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

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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)

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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

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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)

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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.