Six different dose levels were planned. P was weekly escalated from an initial dose of 50 mg/sqm with 10 mg/sqm increments for each step. The aim of the study was to establish the Maximum Tolerated Dose (MTD) and to explore the activity of this combination regimen. Dose Limiting Toxicity (DLT) was defined as: ANC < 500 or PLT < 25,000 for >7 days, ANC < 100 for >3 days, febrile neutropenia or grade 4 non-hematological toxicity in 2/4 patients (pts). From January 1997, 24 pts entered the phase I study; median age was 58 years (range 37–70); ECOG PS 0 = 17, 1 = 6 and 2 = 1; stage IIIB = 6 and IV = 18. Four pts were enrolled at each step. Fourteen and 24 courses were administered at level I and II respectively; 13, 16, 14 and 5 at level III, IV, V and VI respectively. All pts were evaluable for toxicity. No severe non-hematological toxicity occurred: level I G2 neurotoxicity 7%, G2–G3 nausea/vomiting 7%, level II G2 neurotoxicity 4%, level IV G2 hepatotoxicity 6% and G2–G3 nausea/vomiting 12%, level VI G2–G3 nausea/vomiting 20%. Main hematological toxicity was: level I G2 thrombocytopenia 14%, G2 anemia 14%, level II G2 neutropenia 4%, level III G3 neutropenia 15% and G4 afebrile neutropenia 8%, level IV G2 thrombocytopenia 6%, G2 anemia 12%, level V G2 anemia 14%. The preliminary results on the activity of this regimen are encouraging with an overall response rate of 45% (CRs 5%, PRs 40%). DLT has not yet been reached. We are going on with further dose-escalation by 10 mg/sqm increments, in order to establish the MTD of this regimen.

1050 PUBLICATION

Vinorelbine, ifosfamide and cisplatin regimen in inoperable non small cell lung cancer patients

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Introduction: Vinorelbine (VNR), Ifosfamide (IFO) and Cisplatin (CDDP) are considered among the most active drugs for the treatment of non small cell lung cancer (NSCLC). From 01 to 09/98 we have conducted a study with stage IIIB 49% and IV 51% NSCLC patients (pts). They were treated with the schedule: VNR 25 mg/m^2, D1 and D8, IFO 3 gr/m^2, D1 and CDDP 80 mg/m^2 D1 of a 21 day cycle.

Patients and Methods: 115 pts were included with median age 60 ys (27–75); PS: 0–2 (0 = 13%, 1 = 60%, 2 = 27%).

Results: This study is still ongoing and the results obtained from an interim data shows that the total number of cycles administered is 416, with a mean of 3.71 cycles per pt. 84 pts were evaluable for response: CR 1 (1.2%); PR 52 (61.9%); SD 7 (8.3%); PD 24 (28.6%); 5% were performed surgery rescue, mean survival 9.9 months (CI: 269–329, percentile 75). The most limiting toxicity was neutropenia WHO G4 which occurred in 9.5%; with only 0.9% G4 sepsis and one toxic death. Anaemia G3 34%, G4 3%, and other toxicities were moderate.

Conclusion: We can confirm after this preliminar evaluation that this therapeutic scheme is efficient, with acceptable toxicity. The overall survival still has to be defined.

1051 PUBLICATION

Modulation of cisplatin activity by cytosine arabinoside (Ara-C) and hydroxyurea (HU) in the treatment of advanced adenocarcinoma of the lung – A phase II study

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Purpose: The aim of our study is to investigate the possible enhancement of cisplatin activity using short infusional high dose Ara-C plus HU in the treatment of advanced adenocarcinoma of the lung.

Methods: A total of 52 previously untreated patients (pts) with advanced (IIIB and IV) adenocarcinoma of the lung, were included in non-randomized phase II study and were given the following treatment: HU 3000 mg/m^2 plus Ara-C 1000 mg/m^2 2 hours before cisplatin 50 mg/m^2 (D1), followed by cisplatin 30 mg/m^2 (D2–D5), repeated every 4 weeks. Responding pts (CR or PR) received up to six cycles.

Results: 52 pts were evaluable for toxicity, 50 of them for efficacy. The median age was 53 (range 32–72), male/female ratio 37/15, IIIB/IV stage ratio 12/40. Overall 172 cycles were applied (median 3). Partial response (PR) was achieved in 14/50 pts and stable disease (SD) in 25/50 pts. Progresive disease (PD) was registrated in 11/50 pts. WHO grade 3/4 toxicities were: anemia in 19 cycles, neutropenia in 12 cycles, trombocytopenia in 29 cycles and nausea in 3 cycles. Median time to progression was 4 months, for responding pts 5 months (range 1–28), and median survival was 6 months.

Conclusion: 39/50 pts with PR or SD and moderate toxicity of the regimen represent encouraging result. Phase III studies are needed to further evaluate obtained cisplatin modulation.

1052 PUBLICATION

Carboplatin (CBDCA) and paclitaxel (TAX) as induction chemotherapy in stage IIIA–IIIB in non small cell lung cancer (NSCLC)

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Purpose: To determine the efficacy and toxicity of the combination of CBDCA and TAX in stage IIIA(N2)-IIIB NSCLC.

Methods and patients: From January 1998 to January 1999, twenty-one patients with citologically/hystologically proven NSCLC, with clinically stage IIIA(N2)-IIIB (mediastinoscopy and/or PET scan were mandatory for assessment of mediastinal nodes) were treated with a combination of CBDCA AUC 6 and TAX 200 mg/m^2, 3-hours infusion, day 1 every three weeks, for three courses. Local treatment (surgery or radiotherapy) was performed in case of response. Patients characteristics were as follows: median age 66 years (range 51–78), male 21, ECOG PS 1 (range 0–2). Histology: adenocarcinoma 19%, squamous cell 48%, undifferentiated carcinoma 19%, squamous + adenocarcinoma 14%. Stage: IIIAN2 12/21 (57%), IIIB 9/21 (43%).

Results: Up to now 18 patients are evaluable for response. 12/18 patients achieved a partial remission (67%), 5/18 stable disease (28%), 1/18 (5%) progression. Grade 2–3 neurotoxicity was observed in 35% of patients. Grade 3–4 neutropenia and grade 3 thrombocytopenia were observed respectively in 21% and 6% of patients. Subsequently 11/12 responder patients underwent surgery. Radical surgery was possible in 8/11 (73%) patients.

Conclusions: These preliminary results suggest that this regimen is active and tolerable as induction chemotherapy in locally advanced NSCLC. The accrual is ongoing.

1053 PUBLICATION

Combined gemcitabine, ifosfamide and vinorelbine (GIN): Activity and safety of a non-platinum-based regimen in advanced non-small-cell lung cancer (NSCLC)

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In the present phase II study we are evaluating antitumor activity and toxicity profile of a non platinum-based triplet consisting of Gemcitabine (Gem), Ifosfamide (IFX) and Vinorelbine (VNR) in advanced NSCLC; all these three drugs demonstrated interesting single-agent activity in this disease. Untreated pts with stage IIIB/IV NSCLC, WHO PS < 2, bidimensionally measurable disease are elegible for the study. Gem 1000 mg/sqm day 1 and 800 mg/sqm day 4, IFX 3 gr/sqm day 1 (with Mesna), VNR 25 mg/sqm day 1 and 20 mg/sqm day 4 are administered i.v. every 3 weeks. Objective responses (ORs) are evaluated every 2 courses: a maximum of 6 courses are administered in responding pts. According to a Simon's optimal two-stage design more than 4 ORs among the first 19 pts were required to proceed to the second step: a total of 54 pts have been planned. Results concerning the pts enrolled in the first step of the study (19 pts) are as follows: median age 61 yrs (range 45–67); WHO PS 0/1 = 12/7. Stage IIIB/IV = 1/18. Histology: squamous cell 36.8%, adenocarcinoma 47.3%, large cell 15.7%. Total number of courses administered 62, median per pt 3 (range 1–6). Myelosuppression was the most frequent toxicity: neutropenia grade 3/4 = 68%, thrombocytopenia grade 3/4 = 36%; anemia grade 3 = 10%. Four episodes of febrile neutropenia have been reported. Non-hematological toxicity was mild and not clinically relevant. Among 19 pts evaluable for the primary end-point 10 achieved a major response (52.6%; 95% C.I. = 29–75%); all objective remissions were confermed 4 weeks apart and extramurally reviewed. Considering the number of responses observed in the first step of this study the accrual is now continuing at the second stage and, so far, 32 pts have been enrolled.

Supported by a grant from Eli-Lilly.