888

PHASE STUDY: NAVELBINE (N) + ETOPOSIDE (E) + CISPLATIN (C) IN NON OPERABLE NON SMALL CELL LUNG CANCER (NSCLC)

RICHARDET E., LAZARIS C., URIBE A., CARRANZA L., CRESTA C., TOLOCKA H., CASARIN O. - HOSPITAL ITALIANO DE CORDOBA - ARGENTINA

Previous studies have determinated that E + C is an active regimen in NSCLC and provides an overall response rate of 27%. N is a new semisynthethic vinca alkaloid drug with significant activity in NSCLC (about 30% response rate) and breast cancer, so we begun a phase II trial to evaluate synergism of the three drugs. Between 10/91 and 8/92, 33 pts with advanced NSCLC were treated with N 20 mg/m2 day 1 and 8, E: 60 mg/m2 day 1 to 3 and C: 75 mg/m2 day 1. The schema was repeated on day 28. Median age: 55 (r 37-70). Male/female ratio 3:1. Performance status 0:8, 1:13, 2:12. Weight loss: < 10%: 28 pts, > 10%: 5 pts. Stage IIIa: 15%, IIIb: 20% and IV: 65%. Stage IIIa were inoperable due to abnormal cardiovascular or functional respiratory test. **Results:** 20/33 are fully evaluable for R and T. Overall response rate 55% (CR: 0, PR: 11). Median time to progresion: 121 days (r2-239). Overall survival was 170 days (r28-285). T. Grade III-IV according WHO scale was: neutropenia (15%). There weren't any non-hematological toxicity Grade III-IV. There were 2 drug related deaths due to prolongued neutropenia and sepsis. Gastrointestinal and renal toxicity was mild. **Conclusions:** 1) N + E + C is a very active regimen in advanced NSCLC; 2) Neutropenia was dose limitant with 2 drug related deaths. 3) This combination must be explored as neoadjuvant treatment. 4) Hematopoietic colony stimulating factors must be employed in future trials to avoid mielotoxicity.

889

GLUCOCORTICOID RECEPTORS AND GROWTH INHIBITORY EFFECTS OF DEXAMETHASONE IN HUMAN LUNG CANCER CELL LINES

U. Kaiser, J.Hofmann & K. Havemann
Department of Hematology/Oncology, Philipps-University, Baldinger Str., 3550 Marburg, Germany

Glucocorticoid receptors (GR) and growth effects of dexamethasone and the antiglucocorticoid RU-486 were investigagated in 6 cell lines stemming from small cell lung cancer (SCLC) and 13 cell lines stemming from non-small cell lung cancer (NSCLC). All cell lines contained specific and saturable binding sites for the synthetic glucocorticoid dexamethasone, as determined by whole cell and by cytosolic receptor assays. By immunocytochemistry the presence of GR in the cells was conirmed. Among NSCLC cell lines GR was present in large amounts (up to 391fmol/mg) in cell lines stemming from squamous cell carcinoma. In SCLC lines GR was detectable in considerable lower concentrations. Growth inhibitory effects of dexamethasone were seen in 4 NSCLC line. All 4 lines had high GR receptors expression. The antiglucocorticoid RU-486 was virtually inactive when administered alone but exhibited a dose-dependent reversal of the growth-inhibitory effect of dexamethasone. The results indicate an influence of glucocorticoids on the progression of certain types of lung cancer.

890

PHASE II STUDY OF FOTEMUSTINE IN THE TREATMENT OF INOPERABLE NON SMALL CELL LUNG CARCINOMA (NSCLC) : FINAL REPORT

T. LE CHEVALIER(1), A. MONNIER, J.Y. DOUILLARD, J.L. PUJOL, A. RIVIERE, M.L. CERRINA, S. GOUVA, J. BERILLE(2), J.P. BIZZARI(2)
(1) Institut Gustave Roussy, 94800 Villejuif ; (2) I.R.I.Servier, 92415 Courbevoie - FRANCE

Preliminary results had shown promising activity of the nitrosourea fotemustine in advanced NSCLC with a 21 % response rate (RR) in 29 patients (pts) (Monnier et al, ASCO, 1991). This final report concerns a total of 87 pts with locally advanced or metastatic disease.
Protocol : fotemustine as a 1 hour intravenous infusion of 100 mg/m² on D1 and D8. Evaluation was performed after a 5 week rest period according to WHO criteria. Maintenance treatment : fotemustine 100 mg/m² D1 q 3 weeks until disease progression (PD) or toxicity.
77 pts were evaluable for activity : mean age 60 years (33 - 79) ; 66 M / 11 F, mean PS : 75 % (100 - 50), histology : squamous 66.2 %, adenocarcinoma 18.2 %, large cell 15.6 %.
57 pts (74 %) had a metastatic disease including 22 pts with brain metastases (MT), 12 with liver MT, 13 with bone MT. 46 pts had already received a prior chemotherapy.
Response rate (RR) : 1 complete and 12 partial responses (17 % - 95%CI : 8.5 - 25), SD : 21 (27 %), PD : 43 (56 %). Median duration of responses was 22 weeks (7 - 41).
RR according to prior chemotherapy or not was respectively : 5 / 46 (11 %) and 8 / 31 (26 %).
Among the 12 evaluable brain MT, 1 PR and 1 CR were observed.
46 pts received a median number of 3 maintenance cycles (1 - 13) including pts with progressive disease but a subjective response. *WHO grade III - IV toxicity* : thrombopenia in 21 %, leucopenia in 11 %, nausea vomiting in 4.3 %. Hospitalization was only 9 % of the total duration of the on study time. 33 % of the patients never required hospitalization.
Conclusion : despite the poor prognostic factors of this population, fotemustine showed a 17 % RR in NSCLC, with an interesting 26 % RR in pts without prior chemotherapy. Because of the good clinical and biological tolerance, fotemustine can be proposed on a outpatient basis for pts with poor prognostic factors ie with prior chemotherapy or brain MT.

891

PHASE II STUDY OF FOTEMUSTINE - CISPLATIN (CDDP) COMBINATION ON BRAIN METASTASIS OF NON SMALL CELL LUNG CANCER (NSCLC) : INTERIM REPORT

V. TRILLET-LENOIR(1), C. COTO, P.J. SOUQUET, R. RIOU, C. BENOLIEL, J.BERILLE(2)
(1) Hôpital Louis Pradel, LYON ; (2) I.R.I.SERVIER, 92415 COURBEVOIE Cdx - FRANCE

As fotemustine and CDDP cross the blood brain barrier, the combination activity of these 2 drugs was tested on NSCLC brain metastases (MT). 28 patients (pts) entered the study, 16 were evaluable, 3 were not evaluable for activity and 9 too early.
Induction treatment : fotemustine 100 mg/m² D1 and D8 as a 1 h intravenous infusion, CDDP 120 mg/m² D1 and D22 with a 24 h hyperhydradation.
Evaluation was performed by CT scan at D50 according to WHO criteria.
Maintenance treatment : for non progressive pts, fotemustine 100 mg/m² and CDDP 100 mg/m² D1 q 3 weeks.
Characteristics of the 19 pts are 17 M / 2 F, PS 80 % (100 - 50), median age : 56 years (35 - 71), histology : large cell 6 ; squamous 10 ; adenocarcinoma 3. Primary lung disease was revealed by symptomatic brain MT except in 4 cases. All pts have at least one measurable lesion. No pt had received prior chemotherapy. 3 pts had underwent prior lung surgery.
Results : concerning brain MT, 2 complete, 2 minor responses and 5 NC (RR : 12,5 %) and concerning overall responses 4 partial responses lasting from 15 to 24 weeks (RR : 25 %), 5 NC lasting from 10 to 30 weeks, 7 PD were observed. 18 pts were evaluable for toxicity : WHO grade III - IV leucopenia : 4, thrombopenia : 3. Increased plasma creatinin in 4 cases (WHO I : 3 ; WHO II :1). Nausea-vomiting occured during CDDP administration on D1 and D22 (WHO III - IV : 5). 1 pt had a neutropenic related fever. 2 pts had to stop treatment because of toxicity : 1 early and persistant thrombopenia, 1 with uncontrolled mellitus related WHO grade IV vomiting.
Conclusion : fotemustine - CDDP combination shows activity on NSCLC, especially on brain MT. This study is ongoing.

892

QUALITY OF LIFE ASSESSMENT DURING CLINICAL TRIALS : APPLICATION TO THE MULTICENTRE PHASE II STUDY OF FOTEMUSTINE IN ADVANCED NON SMALL CELL LUNG CARCINOMA (NSCLC)

J. BERILLE(1), C. RESSAYRE, J.L. PUJOL, A. MONNIER, J.Y. DOUILLARD, M.L. CERRINA, S. GOUVA, A. LE GROUMELLEC, T. LE CHEVALIER(2)
(1) I.R.I.Servier, 92415 Courbevoie ; (2) Institut Gustave Roussy, 94800 Villejuif - FRANCE

Chemotherapy for patients (pts) with NSCLC remains controversial because of the modest improvement of survival duration. Thus, quality of life is noteworthy to assess the real benefit of a new regimen. 2 quality of life scales have been used during a multicentre phase II study testing fotemustine activity in advanced NSCLC. Among 77 pts, a 17 % response rate (RR) was reported (95%CI : 8 - 25).
Fotemustine was given on D1 and D8 as a one hour intravenous infusion of 100 mg/m² followed by a 5 week rest period. Quality of life was assessed every week during these 6 weeks. The first scale was the quality of life index (QLI) scored from 0 to 10 already tested (Spitzer ; J. Chronic. Dis., 1981). An additionnal new scale was performed measuring 5 somatic variables : appetite, body weight, pain, sleep, fatigue. At each reassessment, these variables were scored as followed : impairment (-1), no change (0) and improvement (+1). The sum of the 5 scores (from -5 to +5) give an original somatic scale (SC).
Results : QLI was fully analysed in 59 pts (77 %) and SC, in 60 pts (78 %). QLI was considered as reliable by investigators for 92 % of the measurements.

	All patients	*Responders*	*No change*	*PD*
n	59	10	19	30
QLI / D0	6.73	7	6.11	7.03
QLI / D43	6.29	6.80	6.89	5.73
p	0.096	0.73	0.05	< 0.001
n	60	10	20	30
SC / D8	0.57	0.50	0.30	0.77
SC / D43	-0.35	-0.20	0.60	-1.03
p	0.001	0.39	0.39	< 0.001

The 2 scales show the same trend : highly significant impairment of quality of live when progression ($p < 0.001$), no change for responders and stable disease. Quality of life of the whole population is worsened due to the progressive pts.
Conclusion : these 2 scales seem feasible and reliable to assess quality of life during this phase II study. In addition, they are very easy to fill by the investigator (less than 10 minutes).

893

EFFICACY AND SAFETY OF GEMCITABINE IN NON SMALL CELL LUNG CANCER (NSCLC)

R Abratt[1], W Bezwoda[2], G Falkson[3], L Goedhals[4], D Hacking[5], T Rugg[6].
[1]Uni of Cape Town, [2]Uni of Witwatersrand, [3]Uni of Pretoria, [4]Uni OFS, [5]Uni of Natal, [6]Lilly, SA.

Gemcitabine, a novel pyrimidine analogue, has activity in a wide range of chemoresistant solid tumors, including NSCLC. In this study, 84 patients with locally advanced or metastatic pathologically documented NSCLC were enrolled. Patients had bidimensional measurable disease defined by CT scan or chest x-ray. Gemcitabine was administered once-a-week for three weeks followed by a week of rest, this constituting one cycle. Initial dose was 1000mg/m² (53 patients) or 1250 mg/m² (31 patients). Patients received 2 25% dose escalations according to tolerance. All responses were strictly validated by an independent review board. Patients (23% female; 77% male; mean age 58 years) had performance status PS1 (97%) or PS0 (3%); 18% had received previous treatment as surgery (12%) or radiotherapy (8%). 70 patients were evaluable for efficacy: overall response rate was 20% (95% CL 11-29%) with 12 (17%) partial responses and 2 (3%) complete responses. Toxicity profile was surprisingly mild with WHO grade III and IV myelotoxicity occuring with 0.3% of doses. Grade III and IV thrombocytopenia occured with 0.2% of doses. Non-haematological toxicity was minor and easily controlled: pedal oedema, asthenia and transient malaise were the most frequently observed side effects. This study confirms gemcitabine's efficacy in NSCLC and modest toxicity profile. The low toxicity and unique mode of action support the evaluation of gemcitabine as combination therapy.