1041 PUBLICATION

Phase II study of docetaxel and cisplatin in first line treatment of disseminated small cell lung cancer (SCLC): Preliminary results

J.A. Moreno[1], P. Lianes[2], F. Cardenal[3], I. Sevilla[4], R. Garcia[5], C. Pallares, B. Gonzalez, J. Gonzalez. *[1]Virgen del Rocio Hospital, Oncology, Sevilla; [2]12 de Octubre Hospital, Oncology, Madrid; [3]Institut Catala d'Oncologia, Oncology, Barcelona; [4]Virgen de la Victoria Hospital, Oncology, Malaga; [5]Gregorio Maranon Hospital, Oncology, Madrid, Spain*

Introduction: Docetaxel (D) has shown activity in SCLC. Its combination with cisplatin (CDDP) has been investigated in phase I trials. We combined D with CDDP in a phase II study to evaluate response rate and toxicity.

Methods: Eligibility criteria included patients (pts) with disseminated disease, non-CNS metastases, without previous chemotherapy and/or radiotherapy. Karnofsky performance status (PS) >= 60%, measurable or evaluable disease, normal bone marrow, liver and renal function and no symptomatic peripheral neuropathy. Pts received D 75 mg/m^2 and CDDP 75 mg/m^2 on day 1 q3wks. Premedication included dexamethasone; G-CSF was allowed if grade IV neutropenia was documented in previous cycle.

Results: To date 27 pts have been enrolled, all evaluable for toxicity and 24 for response; 2 toxic deaths prior to evaluation (1 septic shock, 1 pending further clarification), 1 pt did not reach 3rd cycle. Pts characteristics: median age 61 (36–70) years, all males, 78% had 2 or more involved sites (14 hepatic, 14 distant nodal, 9 contralateral lung, 10 bone, 6 suprarrenal, 4 bone marrow, 6 others), PS < 90% 13 pts, PS >= 90% 14 pts. Median cycles number: 5 (1–6). Total cycles number: 116. Median D and CDDP relative dose intensity was 100%. 4 pts received G-CSF in different cycles. Toxicity: NCI grade III–IV neutropenia, 12/27 pts (44.4%); febrile neutropenia, 6/27 pts (22.2%); 3 pts experienced grade III–IV pulmonary infection. Severe or grade III–IV non hematological toxicities were: alopecia 9 pts, astenia 2 pts, fluid retention 1 pt, nausea-vomiting grade III 2 pts, diarrhea grade IV 1 pt, neuro-motor toxicity grade III 1 pt, allergy grade III 1 pt. Responses: 24 pts evaluable, 1 complete remission, 13 partial remission (overall response rate in evaluable pts 58% [36–78%, 95%CI]), 3 disease stabilization and 7 progressive disease.

Conclusion: D + CDDP combination is an effective regimen in pts with disseminated SCLC (58% overall response rate), in spite of poor disease features (poor PS and multiple metastatic sites). The main toxicity is hematological, with a mild non hematological toxicity. The study is ongoing and updated results will be presented at the meeting.

[1] Santa Creu i Sant Pau Hospital, Barcelona, Spain.
[2] Rhone-Poulenc Rorer S.A., Madrid, Spain.

1042 PUBLICATION

Preliminary report on gemcitabine (G) – Ifosfamide (I) – Cisplatin (P) phase I/II trial in patients with advanced non small cell lung cancer (NSCLC)

H. Bourgeois, D. Lemerre, V. Chicoyneau, T. Paitry, S. Chieze, F. Fruge, F. Boita, J.C. Meurice, A. Daban. *Regional University Hospital La Milétrie, BP 577, 86021 Poitiers, France*

Purpose: to define the MTD of G in combination with I and P, and to assess its activity in pts with advanced untreated NSCLC.

Treatment: G (over 30 mn) at increasing doses from 1 g/m^2 to 2.5 g/m^2 on d1 and d15, I (over 24 hrs ambulatory pump) at 3 g/m^2 on d1, P (over 2 hrs) at 80 mg/m^2 on d15, q4 wks.

Patients: 15M, median age 54 ys (36–70), median PS: 1 (0–2), 2 pts stage IIIA, 2 IIIB, 11 IV. Histology: 11 squamous, 2 adenocarcinoma, 2 large cells.

Results: Since August 1998, 15 pts have been enrolled and have received 40 cycles (Cy). Efficacy (WHO) and hematological toxicity are shown below. Clinical toxicity was mild with no G 3–4 (except alopecia), and no toxic death or encephalopathy.

Dose level	G mg /sqm	N Pts/Cy	Eval Pts/Cy	G 3–4 pts/cy Neutro	Plat	Efficacy (WHO) CR	PR	SD	PD
I	1000	6/17	6/17	3/4	–	0	4	0	2
II	1250	3/15	3/12	1/1	–	0	1	1	1
III	1500	3/9	3/8	2/4	–	1	1	1	0
IV	1750	3/5	0/3	1/1	–	not yet assessable			

Conclusion: 7/12 (58%) evaluated pts had an objective response confirming the activity of this well tolerated regimen. Dose escalation continues and once the MTD and recommanded dose level are determined the trial will continue in randomized phase III trial (GIP low dose versus GIP high dose).

1043 PUBLICATION

Phase I study of docetaxel in combination with gemcitabine as first line chemotherapy (CT) in patients with metastatic non-small cell lung cancer (NSCLC)

S. Bildat[1], U. Gatzemeier[3], M. Reck[3], A. Harstrick[1], W. Eberhardt[1], W. Achterrath[2], C. Krauss[2], H.J. Wilke[1]. *[1]University Essen, West German Cancer Center, Essen; [2]Rhône-Poulenc Rorer, Oncology, Cologne; [3]Krankenhaus Grosshansdorf, Hamburg, Germany*

Introduction: Docetaxel (D) and Gemcitabine (GEM) are two of the most active single agents in the treatment of NSCLC. The minimal overlapping non hematological toxicity of both drugs and the low hematological toxicity of GEM suggest that D + GEM can be combined at dosages near the recommended doses of the single agents. Based on this background the combination D + GEM has been investigated as first line CT in patients with metastatic NSCLC. GEM was given on days 1 and 5 i.v. over 30 min., followed by D given as i.v. infusion day 1 every 21 days.

Methods: Starting dose was: GEM: 800 mg/m^2 i.v. d 1 + 5 and D 60 mg/m^2 i.v. d 1;

2nd dose level was GEM: 900 mg/m^2 i.v. d 1 + 5 and D 60 mg/m^2 i.v. d 1;
3rd dose level was GEM: 900 mg/m^2 i.v. d 1 + 5 and D 75 mg/m^2 i.v. d 1;
4th dose level was GEM: 900 mg/m^2 i.v. d 1 + 5 and D 90 mg/m^2 i.v. d 1.

Results: 24 pts. have been entered on 4 different dose levels and received 74 cycles. M/F: 19/5. Median age was 60 (49–72), median WHO PS 1 (0–2). Neutropenia grade 3 + 4 had been observed at all dose levels but was never dose limiting. The MTD has been reached at dose level 4 with diarrhea and vomiting NCI-CTC grade 3/4 in 3 out of 6 pts. Therefore dose level 3 was recommended dose for phase II studies. In 21 response evaluable pts. 7 PR were achieved.

1044 PUBLICATION

Adm. of vinorelbine encapsulated in anti-HER2 bearing immunoliposomes induces p53 indept. PCD in chemoresistant NSCLC via activation of MEKK1/SEK1/JNK/AP1 pathw

J. Giannios, P. Ginopoulos. *Dept. of Clin. Oncol., Peripheral Hospital of Patras 'St. Andreas', Greece*

Purpose: Overexpression of c-erbB2 and p53 is a common alteration in NSCLC inhibiting PCD after chemotherapy. In this study, we attempt to induce PCD in chemoresistant NSCLC with vinorelbine encapsulated in anti-HER2 bearing immunoliposomes.

Methods: NSCLC biopsy was obtained with FNA from a patient with advanced chemoresistant NSCLC. This carcinoma possessed near tetraploid DNA content, and proliferation index was high. Tumour cells were isolated by the collagenase method, and they were treated with Fab fragments of humanised MAbs antiHER2-IgG bearing fusogenic pegylated immunohposomes with encapsulated vinorelbine. IHC & Northern blot were used for measuring protein-expression and mRNA of p53, c-erbB2, MEKK1, SEK1, JNK and AP-1 pre- and post-treatment. Morphological signs were examined by transmission electron microscopy. Cell cycle was monitored by flow cytometry.

Results: Post-treatment measures of MEK1, SEK1, JNK and AP-1 exhibited upregulation, while c-erbB2 was downregulated compared to pre-treatment assay measures. Expression of p53 due to mutations within N-terminus (AA 46–55) remained enhanced. During treatment, there was antigen-antibody recognition, where anti-HER2 antibody-lipid-drug complexes bind specifically with target antigenic HER2 receptors of the tumour's surface. Subsequently, the outside liposomal bilayer fuses with plasma membrane of tumour cells releasing microtubule inhibitor-vinorelbine in the cytoplasm. After treatment there was depolymerization of microtubules blocking cells in G2/M phase of the cell cycle. Morphological signs of apoptotic irreversible stages F and D2 were exhibited, leading to the formation of apoptotic bodies which were endocytosed by the adjacent tumour cells.

Conclusion: We achieved to reduce p53 indept.-apoptosis in chemoresistant NSCLC by activating the MEKK1/SEK1/JNK/AP-1 pathway. Thus, we believe that the synergestic action of anti-HER2 antibodies and vinorelbine might find a future clinical application against chemoresistant NSCLC, which express significant levels of HER2 and p53.