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A feasibility study of vinorelbine (VNR) and gemcitabine (GEM) in inoperable stage IIIb–IV NSCLC

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Purpose: VNR and GEM have significant activity in NSCLC, both as single agents (RR = 21–30%) and in combination with cisplatin (RR = 30–40%). This Phase I–II trial aims to evaluate the response to concurrent VNR and GEM, as well as response duration, time to progression, survival and toxicity.

Methods: Patients (pts) initially received VNR 30 mg/m^2 weekly on days 1, 8, 15 and 22 of a 28 day cycle, and GEM at 1000 mg/m^2 on days 1, 8 and 15. Initial treatment consisted of 3 cycles with pts achieving NC/PR/CR being given a further 3 courses, and those with PR/CR after 6 courses continuing the treatment until relapse. Entry criteria include histologically or cytologically confirmed Stage IIIb or IV NSCLC, no previous chemotherapy or radiotherapy, PS $\leq$ 2, and informed consent.

Results: Haematological toxicity (neutropenia) has necessitated reductions or delays in the administration of VNR and/or GEM in the first 7 patients. Overall dose intensity has been reduced to 70%. We have therefore modified the schedule to VNR 30–35 mg/m^2 and GEM 1000–1200 mg/m^2 on days 1 and 15 of each 28 day cycle. This fortnightly schedule allows the full protocol dose to be administered as well as being very convenient and cost-effective. The first two cycles of the new schedule have only caused minor toxicities. Two responses have been recorded in the 7 patients who have received $\geq$3 cycles of VNR and GEM. The completed Phase I–II results will be presented.

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p53 mutations in lung cancers of former german uranium miners

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Purpose: Taylor (Lancet 343, 1994, 86) reported about hot spot mutations at codon 249 of the p53 gene in lung cancers of former uranium miners in the USA. We started an investigation in order to get more knowledge about similar mutations in former German uranium miners.

Methods: Until now we investigated 21 former German uranium miners with lung cancers (17 squamous cell cancers). Tumor tissue was investigated by PCR and sequencing for p53 mutations (exons 5–8).

Results: We found no mutation at codon 249 of p53. There were mutations and one deletion in the tumor tissues of 4 patients: codon 154/2: G→T; codon 213/3: A→G; codon 266/1: G→A; codon 272: deletion of 4 bases. Three of the patients were smokers, the G→T transversion was in a nonsmoker.

Conclusions: Our results do not confirm a hot spot mutation in exon 7 of p53 in lung cancers of former German uranium miners. The study is still ongoing.

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First line treatment of advanced non-small cell lung cancer with doxetaxel and cis-platin: A multicenter phase II study

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Purpose: To evaluate the efficacy ans safety of a docetaxel-cisplatin combination in patients with advanced non-small-cell lung cancer (NSCLC).

Methods: Eligibility criteria included chemotherapy-naive patients, with histologically confirmed, measurable, stage IIIB or IV NSCLC, a WHO performance status between 0 and 2, adequate hematologic parameters, and adequate renal, hepatic and cardiac function. Patients received docetaxel (100 mg/m^2) over 1-hour infusion on day 1 and cisplatin (80 mg/m^2) over 30-min infusion with appropriate hydration on day 2. Granulocyte colony-stimulating factor (G-CSF: 150 μg/m^2, SC) was given on days 5–15. Treatment was repeated every 21 days for a maximum of 9 courses or until disease progression.

Results: Fifty three patients were enrolled (28 with stage IIIB and 25 with stage IV disease); all were assessable for toxicity and 50 for response. Grade 3/4 granulocytopenia occurred in 23 patients, 15 of whom were hospitalized for neutropenic fever and 2 died from sepsis. Grade 2 neurotoxicity was observed in 6 patients and grade 3 in 5 patients; grade 3 fatigue occurred in 7 patients, grade 3/4 mucositis in 4 patients and grade 3/4 diarrhea in 6 patients. Mild allergic reactions were observed in 5 patients and mild edema in 4 patients. One complete and 23 partial responses were obsserved (ORR· 48%: 95% C.I.: 34.1–61.8%). The median time to progression was 36 weeks and the median survival time was 56 weeks: the probability for 1-year survival was 58%. The median dose intensity was 30 mg/m^2/week for docetaxel and 24 mg/m^2/week for cisplatin, corresponding to 91% and 89% of the protocol planned doses, respectively.

Conclusion: The docetaxel-cisplatin combonation is an active regimen in advanced NSCLC, with leucopenia being the main toxicity, despite the prophylactic use of G-CSF.

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An overview of 3 phase II trials of navelbine (NVB), and fractionated doses of cisplatin (CDDP) in the management of advanced non-small cell lung cancer (NSCLC)

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Aim: The combination of NVB and CDDP has shown statistically superior survival compared with standard therapy (JCO 1994, ASCO 1996). 3 phase II studies were conducted to assess a new schedule of this combination which can be given on an out-patient basis: NVB 25 mg/m^2 (1 trial 30 mg/m^2) on day 1 & 5 and CDDP 20 mg/m^2 daily over 5 days (D1–5) every 21 days, (maximum 6 cycles). **Results:** Between 7/94 and 2/96, 127 (pts) were included: median age 60 (34–75). 112 (88%) males; PS 0, 1 and 2, 16%, 55% and 27% respectively. squamous cell – 56%, adenocarcinoma – 36% and large cell – 8%; 12% stage IIIA, 36% stage IIIB and 49% stage IV and 3% unknown (metastatic). 471 courses were administered (median 4, range 1–8). WHO grade (G) 3–4 neutropenia – 12%; G3–4 infection episodes 1.4% of courses. G3 nausea/vomiting: 18% (5.4% of courses). Only 4% of pts developed WHO grade 3 constipation and grade 3–4 peripheral neuropathy was observed in 9% of pts (2.4% G 4). G3 alopecia – 12%. The **overall response rates** observed in Brazilian, Polish and Turkish studies are 46%, 47% (N 30 mg/m^2) and 29% respectively; median TTP: 7.4 months and median survival is: 9.2 months **Conclusion:** These results confirm that NVB + CDDP in combination have constant and reproducible high antitumour activity in NSCLC. This new schedule seems well suited for use in the out patient management of NSCLC.

1070 PUBLICATION

Dose scheduling & drug tolerability in phase II studies of gemcitabine and cisplatin chemotherapy for non-small cell lung cancer

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Purpose: To evaluate the influence of scheduling on drug tolerability.

Methods: In 5 phase II studies in NSCLC, gemcitabine was given at 1000 mg/m^2 on days 1, 8 and 15 and cisplatin was given as shown in the Table at 100 mg/m^2 or 30 mg/m^2 (1 study).

Cisplatin given	d1	d2	d15	d15	d1, 8, 15
Med gem dose mg/m^2	718	824	872	957	800
Med cis dose mg/m^2	98	100	94	98	28 × 3
Patients entering cycle (% receiving full dose of gemcitabine)					
Cycle 1	30 (27)	48 (54)	53 (79)	60 (93)	NA
Cycle 2	23 (35)	43 (44)	42 (71)	52 (83)	NA
Cycle 3	18 (22)	37 (38)	35 (77)	45 (64)	NA
Granulocytopenia G4%	13	9	19	20	24
Thrombocytopenia G4%	20	27	8	7	12
Response rate %	33	54	52	38	30
Median survival (mo).	8.4	15 4	13	10.2	8.4
1 yr survival prob %	37	59	55	40	30