1077 POSTER

PROSPECTIVE ASSESSMENT OF CANCER INCIDENCE AND ANTIPYRINE METABOLISM

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Our previous studies revealed faster metabolism of antipyrine among lung cancer patients and their first degree relatives in comparison with subjects without cancer history in their families.

Among 95 relatives of 27 lung cancer patients and 277 controls cancer morbidity during the period of eight years was analysed.

Forty-two subjects from lung cancer families and 55 subjects from control families had previously assessed antipyrine metabolism.

Two lung cancer cases and 8 non tobacco related cancers were noticed in lung cancer families. In the control group no one developed lung cancer. Also one case of tobacco related cancer and 11 cases of non tobacco related cancers were noticed in controls.

The relatives of lung cancer patients in whom lung cancer was diagnosed had very fast antipyrine metabolism. The possible risk for lung cancer in families of lung cancer patients and connection with antipyrine metabolism were discussed.

1078

RANDOMIZED COMPARISON OF ETOPOSIDE-CISPLATIN VS ETOPOSIDE-CARBOPLATIN AND IRRADIATION IN SMALL CELL LUNG CANCER (SCLC): EVALUATION OF LONG TERM SURVIVAL

see page 22

1079 POSTER

GEMCITABINE PLUS CISPLATIN IN NON-SMALL CELL LUNG CANCER: A PHASE II STUDY

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In view of the poor current treatment options for metastatic non-small cell lung cancer (NSCLC), there is a clear need for new drugs and combination chemotherapy regimens in this disease. Single-agent gemcitabine has reproducibly produced objective response rates of 20%– 26% in NSCLC in 5 studies worldwide. Cisplatin is a commonly used component of combination chemotherapy regimens in NSCLC. Cisplatin and gemcitabine have been shown to be synergistic in preclinical models. The Hoosier Oncology Group in Indiana conducted a phase II study using gemcitabine combined with cisplatin in metastatic NSCLC. Cisplatin 100 mg/m^2 was administered on day 1 and gemcitabine 1000 mg/m^2 on days 1, 8 and 15 with cycles repeated every 4 weeks up to 6 courses. Thirty patients were entered from February to October 1994, and 26 patients are fully evaluable for toxicity, response and survival. Eligibility requirements included no prior chemotherapy, Karnofsky PS $\geqslant$ 80, measurable disease, and adequate renal, hepatic and bone marrow function. Radiotherapy was permitted at sites other than the measurable lesion(s). Patient characteristics were: 17 male, 9 female; median age, 62 years (range 37–74); median KPS 90. *Histology:* 10 squamous, 10 adenocarcinoma, and 6 large cell. 21 of 26 patients had stage IV and 5 had stage IIIb disease. Eight patients received prior radiotherapy (2 CNS, 1 bone, 5 chest). Toxicity has primarily been haematological, with frequent need to omit doses of gemcitabine on days 8 and/or 15. There were 11 responses in 26 patients for an overall response rate of 42%. This is the highest response rate recorded in a Hoosier Oncology Group NSCLC study. We conclude that cisplatin plus gemcitabine is an active and well-tolerated regimen in advanced NSCLC. We plan to compare this regimen to single-agent cisplatin (100 mg/m^2 every 4 weeks) in a phase III study.

1080 POSTER

PHASE I TRIAL OF GEMCITABINE (GEM) AND CISPLATIN (CP) FOR NON-SMALL CELL LUNG CANCER (NSCLC)

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This study was undertaken to determine maximum tolerated doses of GEM and CP given weekly ×3 with one week rest. Patients $\leqslant$75 yrs were eligible if they had stage III/IV NSCLC, life expectancy $\geqslant$12 weeks, Hgb $\geqslant$10 g/dl, AGC $\geqslant \times 10^9$/L, platelets $\geqslant 100 \times 10^9$/L, AST and ALT $\leqslant 3 \times$ normal, and creatinine $\leqslant$130 mmol/L. There were 33 male and 17 female pts, median age 62 years (30–75). There were 35 adenocarcinomas, 8 squamous, 6 large cell and 1 mixed tumor. 16 patients were stage III and 34 stage IV tumors. Drug doses, toxicity and response are summarized below:

Dose mg/m^2		No.	Nadir count		ECOG 3/4 toxicity		Response
GEM	CP	of pts	Cycle 1		Cycles 1 to 4		PR/evaluable
			grans	platelets	grans	platelets	
1000	25	7	3.9	151	43/14	14/0	3/7
1000	30	6	2.1	130	33/0	33/17	2/5
1250	30	7	1.6	87	43/29	50/17	0/7
1500	30	7	2.1	142	29/29	67/33	3/7
1750	30	6	1.2	60	33/0	67/17	2/5
2000	30	9	0.7	73	67/33	46/33	2/9
2250	30	8	1.2	60	61/36	57/25	1/7

Response rate was 30% (CI 17–43%), median duration 20 weeks. Dose limiting toxicity in Cycle 1 was not seen at any level, but after Cycle 2, cumulative myelotoxicity necessitated frequent dose reductions at high GEM doses. Thus GEM 1500 and CP 30 will be used for Phase II study. Supported by Eli Lilly, Canada.

1081 POSTER

GEMCITABINE COMBINED WITH CISPLATIN IN NON-SMALL CELL LUNG CANCER (NSCLC): A PHASE I/II STUDY

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Gemcitabine (GEM), a novel nucleoside analogue, and cisplatin are among the most active single agents in the treatment of NSCLC, producing reproducible response rates of approximately 20%. The two drugs are attractive candidates for combination: dissimilar modes of action with preclinical evidence for potential synergistic tumour cell killing, and largely non-overlapping side-effect profiles. This phase I/II study was designed to determine the maximum tolerated dose of cisplatin in the combination up to a predetermined maximum of 100 mg/m^2, and safety and efficacy. GEM 1000 mg/m^2 was given as a 30 minute iv infusion weekly × 3 repeated every 4 weeks. Cisplatin was given immediately after the 3rd infusion of GEM in each cycle. In the phase I portion of the study cisplatin was escalated from 60 to 75 to 100 mg/m^2 in successive cohorts of 3 patients, using an adaptive control algorithm. Further patients were then accrued into the phase II portion of the study and treated at 100 mg/m^2 cisplatin. Patients treated at 100 mg/m^2 cisplatin in the phase I portion of the study were also evaluable for response. Characteristics of all 66 patients recruited were: males 55, age range 39–74. PS: 0 in 4, 1 in 55, 2 in 7. *Histology:* adenocarcinoma 22, squamous 32, large cell 11, unspecified 1. Stage: IIIa in 2, IIIb in 41, IV in 23. Toxicity was easily managed at 100 mg/m^2 cisplatin (data currently available for 55 patients and 236 courses). The incidence of combined worst WHO grade 3 and 4 toxicities per patient was: neutropenia 51%, thrombocytopenia 25%, ALT/AST 2%, alopecia 2% fever 4%, nausea and vomiting 50%. Neutropenia and thrombocytopenia were both of short duration and uncomplicated. No serious renal toxicity was seen. 52/60 eligible patients were evaluable for response assessment in the phase II portion of the study. 20 PRs were seen, for a response rate of 38%. This combination of gemcitabine and cisplatin is well tolerated with promising activity. Further trials are required to assess whether the schedule used is optimal.

1082 POSTER

ON LINE ELECTRONIC PORTAL IMAGING IN LUNG IRRADIATION: USEFULNESS IN CORRECTION AND DEFINITION OF ANATOMICAL LANDMARKS

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We studied the usefulness and feasibility of on line electronic portal imaging (EPI) with intra fractional correction of table position in the irradiation of lung cancer.

Antero-posterior (AP) and oblique anterior (OA) fields of 160 sessions from 8 patients were evaluated before and after correction.

For the AP fields the errors in positioning (longitudinal, lateral and rotational) were measured using the in-house developed OPIDUM system, using lung tops and carina as anatomical landmarks. After correction of the table position the rest of the fraction dose was administered

and residual errors were measured using the same technique. For OA fields only the set up error was measured.

In AP irradiation the positioning error before correction is more important than the movements due to breathing. Overall systematic and random error were respective −0.8 (−5.36 to 4.53) mm and 4.5 (1.1 to 3.7) mm for longitudinal position and −3.3 (15.8 to 4.5) mm and 7.0 (0.8 to 3.2) mm for lateral position. After correction we found 0.6 and 2.4 mm for longitudinal and −0.02 and 1.6 mm for lateral position as residual systematic and random errors. Rotational errors were comparable before and after correction, ranging from −1.4 to 0.5° (syst.) and 0.9 to 1.9° (random) before and −1.6 to 1.2° (syst.) and 0.5 to 2.2° (random) after correction.

For OA fields there was a tendency to larger systematic errors in longitudinal and lateral position, the random errors were comparable. For rotational errors, both types of errors were increased compared to AP fields.

As a result of this study the patient positioning technique was changed to reduce the variation of the position of the head support in respect to the patients body, which may have a large influence on positioning errors.

1083 ORAL

A COMPLETED PHASE I/II TRIAL OF NEOADJUVANT CHEMOTHERAPY (CT) WITH CISPLATIN AND VINORELBINE FOLLOWED BY ACCELERATED THORACIC IRRADIATION, (TRT) IN INOPERABLE NSCLC

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Goal: To improve local control by accelerating the delivery of TRT. *Design:* Inoperable and measurable stages II, III-A and B NSCLC, KS ⩾70. Prior weight loss allowed. *Treatment:* cisplatin 100 mg/m^2 week 1 and 5, vinorelbine 30 mg/m^2 weekly × 5 (15 mg/m^2 on week 2 followed by TRT, 30 fractions of 2 Gy in four weeks, once daily weeks 1 and 2, BID weeks 3 and 4 (same biological dose as 30 daily fractions of 2 Gy). *Results:* From 11–92 to 11–94, 42 eligible patients entered and 39 are evaluable. Response rate 46.2% (18/39) after CT and 71.8% (28/39) after TRT. 24 patients have progressed (1st relapse: 6 in RT field, 16 outside RT field [7 in brain], 2 unknown), and 20 have died. Actuarial median survival 12.0 months. ⩾ grade III toxicities post TRT in 23.1% (9/39:7 oesophagus [1 grade 5], 1 lung, 1 skin). Median weight loss during treatment was 2.5 kg. *Conclusions:* Cisplatin and vinorelbine is an active induction CT regimen. Accelerated TRT to 60 Gy is well tolerated and may yield better local control than standard TRT.

1084 POSTER

INTERIM RESULTS OF A PHASE II TRIAL OF DOCETAXEL IN COMBINATION WITH CISPLATIN IN PATIENTS WITH METASTATIC OR LOCALLY ADVANCED NON-SMALL CELL LUNG CANCER (NSCLC)

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Docetaxel (Taxotere®; T), a semi-synthetic taxoid has considerable single agent activity in NSCLC with a response rate of 38% (Francis *et al.*, *JCO*12; 1232, 1994). We recently reported the results of a phase I trial of T in combination with cisplatin (P) in patients (pts) with metastatic or locally advanced NSCLC. For phase II trials, the recommended dose of each agent administered as a 1 hr infusion was 75 mg/m^2 (*Ann. Oncol.* 5; P773, 1994). Hydration was started 2 hrs prior to T which was given immediately prior to P and ended 22 hrs post P. Ondansetron and dexamethasone were given as antiemetics. Cycles were repeated each 21 days. Eligibility included locally advanced/metastatic NSCLC, no prior chemotherapy, measurable disease, age 18–75 yrs, WHO performance status (PS) 0–2 and adequate bone marrow, hepatic and renal function. CSF's or prophylactic antibiotics were not permitted. Interim results, as analysed on 9/3/95 are reported. Baseline characteristics for the 47 eligible patients (2 pts with Stage 1 disease were excluded from response analysis) were median age 60 (range 36–74) years, PS 1/2 of 61%/22% and Stage III/IV, 37%/63% pts respectively. All pts were evaluable for toxicity but only eligible pts completing 2 cycles of chemotherapy were evaluable for response. In 36 evaluable pts, the partial response (PR) rate was 33% (12/36 pts), SD 44% (16/36 pts) and PD 22% (8/36 pts). Of the 12 PR's, 6 have been confirmed on subsequent CT scans. Grade 4 toxicities included febrile neutropenia (3 pts), neutropenia (31 pts) and diarrhea (5 pts). Grade 3 or 4 nausea/vomiting was seen in 10 pts. Other toxicities requiring dose reductions or discontinuation of study medication included cardiac abnormalities (2 pts) and fluid retention (2 pts). There were 9 hypersensitivity reactions. There was 1 toxic death (infection and neutropenia). Although significant toxicities were observed, these were manageable. Final results will be presented. The combination of docetaxel and cisplatinum has significant activity in NSCLC although does not appear to be substantially better than T alone. Toxicity may preclude phase III evaluation.

1085 POSTER

LUNG CANCER EPIDEMIC IN RUSSIA

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Lung cancer is by far the most frequent cancer cause of death in Russia. One-third of all male cancer deaths are due to lung cancer. In males high risk areas with age-standardized incidence rates (world standard population) per 100,000 person-years (ASIR) being higher than 90.0 are scattered across Northern Russia, Oural, South-West and Far-East Siberia. ASIR ranging from 90.0 to 120.0 are recorded in more than twenty cities and large towns. Lung cancer incidence rates in women are not very high, a very similar situation to that in most other countries. High risk areas, ASIR ranging from 15.0 to 26.0 are in East- and Far-East Siberia. In large cities and towns with very high rates of lung cancer male/female ratios of incidence range between 4.0 and 17.0, while in most areas urban/rural ratio for both male and female is about 1.0–1.5. 94% of lung cancer death in males and 48% in females in Russia are attributed to smoking. Prevalence of smoking in males have reached in some areas 70–80% and has leveled, while smoking in women is increasing. This trend predicts that the epidemic of lung cancer in women will probably reach in Russia the same size as in men.

1086 PUBLICATION

A PHASE II STUDY OF GEMCITABINE WITH CISPLATIN IN PATIENTS WITH NON-SMALL CELL LUNG CANCER

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In a phase II study of patients with locally advanced or metastatic non-small cell lung cancer (NSCLC), gemcitabine was given at a dose of 1000 mg/m^2 weekly for 3 weeks (days 1, 8 and 15 followed by a 1 week rest) and cisplatin was given at a dose of 100 mg/m^2 on day 15 with gemcitabine—this all consisting of 1 cycle of chemotherapy. The patients had no prior chemotherapy, were WHO performance status 0–2 and all had measurable disease on CT scan. To date, 38 patients are available for analysis of whom 35 are evaluable for a response as they have received at least 1 cycle of chemotherapy. All patients are evaluable for toxicity. The mean patient age was 56 years (range, 35–74 years) and the proportion with stage IIIa and IIIb and stage IV disease was 29%, 35% and 36%. The patients received a median of 4 cycles of chemotherapy. A complete response was observed in 1 patient (3%) and a partial response in 15 patients (43%) for an overall response rate of 46%. A WHO grade 1 and 2 increase in serum creatinine, occurred in 11% and 3% of patients respectively. WHO grade 3 and 4 leukopenia occurred in 24% and 0%, and thrombocytopenia in 19% and 3% of patients respectively. These findings are compatible with a higher response rate with the combination of drugs than with either drug singly and with moderate toxicity.