Conclusion: The combined radiochemotherapy was well tolerated. We obtained the same good results with a normofractionated RT with fewer side effects than studies with hyperfractionated RT. The KI and the haemoglobin level at the start of the treatment seem to be the most relevant prognostic factors.

798 POSTER

Impact of third line ZD 1839 therapy on patients with advanced non-small cell lung cancer (NSCLC) who had failed prior platinum and/or docetaxel-based regimens (Astra Zeneca Expanded Access Programme)

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Background: Patients with locally advanced or metastatic NSCLC pretreated with two or three regimens of conventional standard chemotherapy have a median overall survival time of 4 months (Massarelli et al. Lung Cancer 2003). Iressa, an EGFR tyrosine kinase inhibitor, has recently shown a favourable overall tumor growth control (30%) and symptomatic improvement (40%).

Aim: The efficacy of a third line with ZD 1839 as an outpatient salvage treatment was analyzed on the basis of tumor response rates, time to third progression (TTTP), time to death (TTD) and disease-related symptom response.

Patients and Methods: 32 patients who had failed two previous chemotherapy regimens (median age 64; M/F, 69/31%; PS 1/2/3, 50/44/6%, locally advanced/metastatic disease, 69/31%) were treated with oral ZD 1839 250 mg/daily.

Results: An early tumor progression (TTTP <3 months) occurred for a minority of evaluable patients (4/24, 17%). A favourable overall tumor growth control was observed in 20/24 (83%) of the heavily pretreated patients, including partial remissions in 2/24 (8%) (both women with histologically confirmed adenocarcinoma) and stable disease in 18/24 (75%) patients. Median overall time to third progression and TTD evaluated from the beginning of the third line treatment on 13 evaluable patients were respectively of 4 and 6 months. Approximately 80% of patients (13/16) having a time to second progression not lower than 4 months with Docetaxel, had a TTTP with Iressa greater than 4 months. The majority of drug-related adverse events were mild and reversible. Grade 2/3 diarrhoea and skin rash required treatment's discontinuation in only 2 patients (8%). Performance status (Karnofsky Scale) scores decreased in 10/32 patients (31%), allowing to reduce the analgesic use.

Conclusion: Our experience confirms Iressa's activity and acceptable toxicity. A significant correlation was seen regarding second line treatment with Docetaxel and related time to progression. An updated efficacy and toxicity analysis will be presented at the meeting.

799 POSTER

Randomized trial of docetaxel plus cisplatin (DC)versus etoposide plus cisplatin (EC) in locally advanced, recurrent, or metastatic non-small cell lung cancer (NSCLC).

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Background: The aim of this study was to compare DC and EC regimens in terms of response rate, safety profile, and overall survival (OS).

Materials and Methods: From April 2000 to March 2002, 78 patients with locally advanced (LA, Stage IIIB), recurrent (R), or metastatic (M) NSCLC were recruited. Eligibility criteria included: age ≥ 18 years, pathologically confirmed NSCLC, no prior chemotherapy, Karnofsky performance score (KPS) ≥80%, measurable disease, no brain or leptomeningeal metastasis, and signed informed consent.

Patients:

	DC	EC
n	40	38
Median Age (years)	64.5	59.0
Adeno./ Squamous	47.5%/50%	50%/48.7%
LA/ M/ Local R	50%/47.5%/2.5%	42.1%/57.9%/0%
Prior RT/ Surgery (n)	1 /2	0/ 4
KPS	80	80

DC treatment consisted of 75mg/m^2 of both agents given on day 1, every 3 weeks for 6 cycles. EC treatment consisted of 75 mg/m^2 of cisplatin on day 1, and 100mg/m^2 of etoposide on days 1–3, every 3 weeks for 6 cycles.

Results: Thirty-four patients from the DC arm and 33 patients from the EC arm were included in the efficacy analysis. Two patients in the DC arm did not receive treatment; 1 patient withdrew consent and 1 developed brain metastasis. Four patients from the DC arm received the first cycle of treatment but could not be evaluated for response; 1 patient was lost to follow up (f/u), 2 withdrew consent, and 1 died as a result of an accidental fall. From the EC arm, 3 patients withdrew consent, 1 was lost to f/u, and 1 died of cardiac arrhythmias. Adverse events NCI grade ≥ 3 occurred in 32 patients (19 DC/13 EC): neutropenia 4(10.5%)/6(15.8%); febrile neutropenia 3(7.9%)/0; sepsis 1(2.6%)/0; infection 1(2.6%)/0; nausea 2(5.3%)/4(10.5%); diarrhea 2(5.3%)/1(2.6%); fatigue 3(7.9%)/0, alopecia 6(15.8%)/6(15.8%).

Conclusion: DC offers superior response rates over EC and shows a trend in improved median survival in chemotherapy-naïve patients with locally advanced (Stage IIIB), recurrent, or metastatic NSCLC. There was no significant difference in TTP between groups and both regimens were well tolerated.

800 POSTER

The placental growth factor (PlGF) gene is more highly expressed in small cell lung cancers compared to non-small cell lung cancers

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Background: The characteristics of SCLC are that they disseminate in their early stages to distant organs, and that they recur frequently despite initial high sensitivity to chemotherapy and radiation. Differences in the gene expression profiles in small cell lung cancers (SCLC) and non-small cell lung cancers (NSCLC) may explain their different clinical characteristics. The aims of this study were (1) to identify genes differentially expressed in SCLC and NSCLC using mRNA differential display, and (2) to determine the clinical relevance of such genes in lung cancer.

Material and Methods: RNA differential display using three SCLC and six non-SCLC cell lines was used to identify a differentially expressed gene. Differential expression of the gene was confirmed in additional lung cancer cell lines using RT-PCR. Immunohistochemical staining for the gene product was performed on paraffin-embedded tissue from lung cancer patients. We examined the relationship between the expression of the gene and clinical parameters, including disease stage, response to treatment and survival time.

Results: The PlGF gene was identified as preferentially expressed in SCLC compared with NSCLC cell lines using mRNA differential display. Further analysis of 45 lung cancer cell lines using RT-PCR showed that the PlGF gene was expressed in nine of 13 SCLC cell lines (69%) and five of 32 NSCLC cell lines (15.6%) ($P < 0.001$, Fisher's exact test). Immunohistochemistry using anti-PlGF antibody on the paraffin blocks from lung cancer patients showed that PlGF expression was significantly higher in SCLC than NSCLC tissue sections (32% vs 5.6%, $P = 0.041$, Fisher's exact test). Expression of PlGF protein did not correlate with disease stage, response to treatment or survival time in SCLC patients.

Conclusion: The present study suggests there is higher expression of PlGF in SCLC compared to NSCLC. It may be that higher expression of the angiogenic factor PlGF contributes to differences between the progression of SCLC and NSCLC, especially in regard to the nature of SCLC metastasis.

801 POSTER

Oral chemotherapy and upper gastro-intestinal tolerance (UGT) improvement of nausea and vomiting in non-small-cell-lung-cancer (NSCLC) patients (pts) treated with oral navelbine (NVB) and standard antiemetic prophylaxis

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Background: UGT during oral chemotherapy is a constraint which may limit its use in cancer pts. Oral NVB is a new formulation that allows a

similar efficacy to that of intravenous NVB with a dose-equivalence between both formulations demonstrated from pharmacokinetics (PK). The safety profile is almost identical with the exception of more frequent nausea and vomiting, but rarely severe. In order to evaluate the impact of a standard anti-emetic prophylaxis, we compared the UGT toxicity in two NSCLC patient populations treated by oral NVB with/without anti-emetic prophylaxis.

Material and methods: The UGT has been retrospectively analysed from two studies performed in locally advanced or metastatic NSCLC pts receiving NVB oral as a weekly monotherapy at 60mg/m2 for 3 doses, then increased to 80mg/m2 in the absence of grade 3-4 neutropenia. In the 1st study (Ann Oncol 2001;12(10):1375-81), there was no anti-emetic prophylaxis given to the 76 pts treated with oral NVB. In the 2d protocol recently conducted in 56 pts, a systematic anti-emetic prophylaxis was recommended including 5–HT3 antagonists. PK was performed in both studies.

Results: In the 76 NSCLC pts (median age: 64y) without anti-emetic prophylaxis (1st study), nausea and vomiting (CALGB scale) were 83% and 65% respectively; however grade 3-4 were infrequent (10.5% and 7.9% respectively). Median delay between dosing and vomiting was 5 hours with only one occurrence within the 1st hour and 25% vomiting occurring between 2 and 3 hours post dose. Secondary prophylaxis was given to 49% pts (34% with a dopamine antagonist and 14.5% with a 5HT3 antagonist). In the 56 pts (2d study) (median age: 74y) with anti-emetic prophylaxis, 88% received a 5HT3 antagonist. Overall incidence of nausea (54%) and vomiting (24%) were largely reduced compared to their occurrences in the 76 pts without anti-emetic prophylaxis. One pt had grade 3 nausea (2%) and 1 pt (2%) grade 3 vomiting (NCI-CTCv2 scale). No influence of early vomiting (<3h) on NVB oral bioavailability was demonstrated from population PK analysis. The absence of any PK drug-drug interaction between anti-emetics and NVB oral was also well established.

Conclusions: UGT can be controlled in pts treated with oral NVB by a primary anti-emetic prophylaxis with 5HT3 antagonist. This type of prophylaxis is a standard recommendation in the ESMO guidelines. Moreover, neither early vomiting nor associated anti-emetic prophylaxis modify NVB blood exposure.

802 POSTER

Multicenter Phase II trial of weekly Taxol and Paraplatine as first line treatment in elderly patients with non small cell lung cancer (NSCLC): preliminary results

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The use of platinum based chemotherapy in elderly patients with NSCLC is still controversial. The purpose of this phase II trial was to evaluate the efficacy and the safety of 1st line weekly Taxol (T) [paclitaxel] and Paraplatine (P) [carboplatin] in elderly patients with NSCLC.

Eligibility criteria included: age > or = to 70; measurable disease; ECOG PS 0-2; adequate bone marrow, liver, and renal function; no previous chemotherapy; and patient informed consent.

Treatment schedule: T 90 mg/m^2 IV (1h) on days 1, 8 and 15 and P AUC 6 IV on day 1 of a 28-day cycle. Tumor response was evaluated using RECIST criteria and symptoms were evaluated using lung cancer symptoms scale (LCCS).

Results: From March 2002 to March 2003, 51 patients have been included. Data are available for the 40 first patients. They were 29 males and 11 females, median age 74 (range 70-88), ECOG PS: 0 (33%), 1 (56%) and 2 (10%). Tumor histology was squamous cell carcinoma in 13 pts, adenocarcinoma in 23 pts, Large cell Carcinoma in 2. NSCLC was stage IV in 33 pts and IIIb in 7 pts. A total of 156 cycles have been administered (median 4 /pt [range 1-6]). Hematologic toxicity: G3-4 neutropenia in 2 pts (5%) G4 thrombocytopenia in 1 pt (3%) and G3 infection in 2 pt (5%). Non-hematologic toxicity: G3 asthenia in 1 pt (2%), G3 neuropathy in 3 (7%). One toxic death is reported. Objective response was reviewed by an independent committee for 38 first evaluable pts: 1 CR, 17 PR and 12 Stable disease.

Conclusion: Preliminary data suggest that weekly Taxol and Paraplatine is a well tolerated combination with very promising activity in elderly population with NSCLC. Final analysis will be available in September 2003.

803 POSTER

Phase I / II and pharmacokinetic study of Vinflunine (VFL) in combination with cisplatin (CDDP) for treatment of advanced non-small cell lung cancer (NSCLC) in chemonaive patients: Preliminary results.

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VFL (Javlor®) is a novel semi-synthetic vinca-alkaloid obtained through superacidic chemistry by the selective introduction of two fluorine atoms at the 20'position of vinorelbine (VRL). VFL has shown higher in vivo antitumour activity than VRL in several human tumour models. Platinum-based doublets are the standard of treatment in advanced NSCLC and pre-clinical experiment testing in vitro A549 human NSCLC line has shown synergistic effects of VFL in combination with CDDP. This trial was designed to determine the recommended dose (RD) of the combination (phase I) and, its response rate and safety (phase II) in pts with previously untreated advanced NSCLC. Pharmacokinetic blood sampling was performed to study the absence of mutual interaction VFL-CDDP. Three doses of VFL were investigated 250 mg/m*, 280 mg/m* and 320 mg/m* in combination with CDDP 80 mg/m* once every 3 weeks. Due to the absence of dose limiting toxicities in the first 2 doses of VFL (3 pts per dose), the RD was established at VFL 320 mg/m* plus CDDP 80 mg/m*. Accrual is planned for 40 evaluable pts in phase II (at the RD). As of today, 36 are included and results available for 15 pts with Karnofsky's performance status (KPS) 80 to 100%, measurable disease (WHO) and adequate biological functions. So far, 15 pts (13 males, 2 females; KPS 100%: 5 pts, KPS 90%: 7 pts, KPS 80%: 3 pts; median age: 56 years/range 47-70) are evaluable for response and safety. Five out of these 15 patients achieved partial response (independent radiological review) and, 7 had stable disease. The median number of cycles administered was 5. No grade (G) 3 / 4 anaemia or thrombocytopenia were recorded (NCI-CTC scale), neutropenia G 3 / 4 was seen in 52% of cycles and one episode of febrile neutropenia was reported. Other G 3 non haematological toxicities were: constipation and hiccups 1 episode respectively and abdominal pain 2 episodes. Preliminary pharmacokinetic analysis does not evidence any VFL / CDDP interaction.

Conclusions: VFL / CDDP is a highly active combination in first line treatment of advanced NSCLC, with an excellent tolerance profile; the study accrual is ongoing and updated results will be reported at the meeting. Other combination trials in first line NSCLC have started with carboplatin and gemcitabine.

804 POSTER

Navelbine and Cisplatin with concurrent radiotherapy for unresectable stage III NSCLC

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Purpose: There has been conducted a prospective phase II study to determine the response rate (RR), toxicity and survival (S) of concurrent Navelbine and Cisplatin (2 cycles), with radiotherapy, followed by 2 additional cycles of consolidation chemotherapy with the same drugs, for locally advanced stage III NSCLC. In order to decrease toxicity the role of protectors like amifostine has been evaluated.

Methods and materials: Thirty-three patients with histologically proven NSCLC, unresectable stage IIIA and IIIB, PS=1-2, measurable disease, adequate hematologic, renal and hepatic functions were included the study from 16.11.2000 to 20.11.2002, Patient caracteristics were: median age 59, ranging between 45 - 71, M/F=30/3, PS 1/2=13/20, stage IIIA/IIIB=3/30, squamous cell cc 27, adenocc 2, adenoid chistic cc 1, large cell cc 3. Thetreatment consisted of 2 cycles of chemotherapy with Navelbine (15 mg/sqm, d 1,8, q21) and Cisplatin (80 mg/sqm, d 1, q 21), given concurrently with radiotherapy (60 Gy/30 fractions/ 6 weeks), followed by 2 more cyclesof consolidation chemotherapy with the same drugs (navelbine: 25 mg/sqm d 1,8, cisplatin 100mg/sqm, d1, q 21). Fifteen patients received amifostine (Ethyol WR-272) 740 mg/sqm, d1, 8, q 21, which is an organic thiophosphate, found to have radio and chemoprotective effect. Chemotherapy has been completed by 63% and radiotherapy by 94% patients.