87 POSTER

EFFECTS OF PROPHYLACTIC CRANIAL IRRADIATION (PCI) IN SMALL CELL LUNG CANCER (SCLC); RESULTS OF UKCCCR/EORTC RANDOMISED TRIAL

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This multicentre randomised trial was designed to assess the effect of PCI on survival, appearance of cranial metastasis and cognitive function in patients with limited disease and complete response (CR) to induction treatment. At the time of the abstract submission 299 of the planned 300 patients have been randomised. Ninety-seven patients undergone prospective neuropsychometric assessment. All patients received initial chemotherapy and 84% also had thoracic irradiation. Median age at the time of randomisation was 60 (range 28–79) and 64% were male. The current median survival from randomisation is 10 months (95% confidence interval 9–12 months) with estimated survival 43% at one year, 23% at 2 years and 18% at three years from randomisation. Sixty-four patients have been reported as having cranial relapse, KM estimates being 29% at one year, 37% at 2 years and 42% at 3 years from randomisation. The analysis presented at the meeting will include comparisons of rates of survival, cranial metastases and cognitive function between the randomised PCI or no PCI groups at a time when the trial will have been closed for 6 months and 90% of patients will be more than 1 year from randomisation.

88 POSTER

MVP (MITOMYCIN-C, VINBLASTINE AND CISPLATIN) CHEMOTHERAPY IN SMALL CELL LUNG CANCER (SCLC)

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Combination chemotherapies in SCLC produce response rates of 70% + but toxicity may be severe and the overall relapse-free survival rate is just 10–20%. MVP chemotherapy (Mitomycin-C 8 mg/m^2, courses 1, 2, 4 and 6, Vinblastine 6 mg/m^2, Cisplatin 50 mg/m^2) is an active low toxicity regimen in non-SCLC (Ellis *et al.* 1995). We now report the results of our phase II trial of MVP in 50 chemo-naive patients (pts) with SCLC. There were 33 men and 17 women with median age 66 years (range 46–83 years); 18 pts had limited disease (LD) and 32 extensive disease (ED). WHO PS was as follows: 3 pts PS 0, 33 pts PS 1, 10 pts PS 2, 4 pts PS 3. A maximum of 6 cycles were given in responding patients. On completion of chemotherapy pts with LD obtaining CR/good PR received thoracic irradiation and those obtaining CR were offered entry into the ongoing MRC PCI trial. The overall response was 79% with 17% CR and 62% PR. For LD pts there were 38% CR and in ED only 1 pt achieved CR. Median response duration for LD pts was 8 months and for ED pts 5 months. Median survival was 10 months for LD pts and 6 months for ED pts. There was complete resolution of symptoms in 24%, partial improvement in 68%, no change in 2% and progressive symptoms in 6%. Toxicity: 24% developed WHO grade 3/4 neutropenia, 16% grade 3/4 thrombocytopenia, and 6% significant hair loss. Two pts died during the first week of treatment with neutropenic infection. Quality of life using the EORTC questionnaire (QLC-C30) with lung cancer module, demonstrated significant improvements from baseline levels in emotional and cognitive functioning, global QOL, of pain, dyspnoea and cough. MVP, an effective palliative regimen for non-SCLC, is also active against SCLC with low toxicity and merits comparison with more toxic conventional schedules.

89 POSTER

SURGERY AND ADJUVANT THERAPY OF SMALL CELL LUNG CANCER

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In the course of 1957–1993, 1245 patients were treated surgically. In 87 cases undifferentiated carcinoma-small cell carcinoma, anaplastic was confirmed. Forty-five patients received adjuvant therapy: chemotherapy, radiotherapy. In the past three years two courses of chemotherapy were given before surgery. The operation is performed after 50% favourable response. In the cases when the diagnosis of small cell lung carcinoma was confirmed after the operation, the patients were treated with 4 courses of polychemotherapy. The patients with positive lymph nodes (N1 and N2) after chemotherapy receive radiotherapy. We have a control group of patients who did not received any adjuvant therapy (refuse of patients, surgical complications). The follow-up results were better in the group, which had received combined treatment. The best results were observed in the patients, undergoing lobectomy and receiving combined treatment: median survival was 30.3, months, control patients—18.2. In our experience, surgery can be used only in the cases of limited tumor (T1, 2N0 M0). After surgery chemotherapy must be used in all cases (both in negative and positive lymph nodes).

90 POSTER

HIGH-DOSE SEQUENTIAL CHEMOTHERAPY (ICE) UNDER CIRCULATING PROGENITOR CELLS (CPC) PROTECTION IN PATIENTS WITH SMALL CELL LUNG CARCINOMA (SCLC). PRELIMINARY REPORT ON A MULTICENTRIC STUDY

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Starting in February 1994, 20 patients (pt) with a median age of 50 years (range 41–63) from 7 European centers have been included. Complete data were obtained in 16 patients so far. CPC were mobilized with chemo (Epirubicine 75 mg/m^2/d, D1 + D2) followed by G-CSF 5 μg/kg/d for 14 days. HD chemo consisted in 3 sequential courses of ICE regimen (Ifos. 10 g/m^2, Carbo. 1200 mg/m^2 and Etop. 1200 mg/m^2) under CPC protection and G-CSF 5 μg/kg/d. Out of the 16 pt, 12 completed full program (3 cycles). One pt died of septic shock before receiving any ICE course. One pt died during the first ICE of renal insufficiency. Two pt had only 2 courses because of toxicity. Among the 16 pt, response rate (RR) was: 7 CR, 6 PR, 1 PD; 3 pt are not evaluable due to early withdrawal (overall RR: 13/16 = 81%). Thirty-nine cycles of HD chemo were given with a median hematological recovery of 9 days (range 7–12) until neutro. counts > 1.0 × 10^9/l and 9 days (range 7–17) until thrombo. > 20 × 10^9/l. No cumulative, hematological toxicity was seen. Accrual of patients is still ongoing and updated results will be presented.

91 POSTER

DELIVERED DOSE INTENSITY WITH AN INDUCTION CHEMOTHERAPY (CT) BY IFOSFAMIDE, ETOPOSIDE AND ANTHRACYCLIN FOR PATIENTS (PTS) WITH SMALL CELL LUNG CANCER (SCLC): A REPORT BY THE EUROPEAN LUNG CANCER WORKING PARTY

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We conducted a randomized trial comparing a maintenance CT versus a simple follow-up in SCLC pts having achieved a complete response after 6 induction CT courses, given at theoretical 3 week intervals, with ifosfamide (IFO) (1.5 mg/m^2 d1–3, iv), etoposide (VP) (80 mg/m^2 d1–3, iv) and, with a random allocation, epirubicin (EPI) (60 mg/m^2 d1) -IVE- versus adriamycin (ADR) (45 mg/m^2 dl) -IVA- in a first set of pts or epirubicin (60 mg/m^2 dl) -IVE60- versus epirubicin (90 mg/m^2) -IVE90- in a second set of pts. The mean absolute delivered dose intensities (ADI) of the anthracyclin in mg/m^2/week were as following:

	First set		Second set	
	IVE	IVA	IVE60	IVE90
At 3 courses	n = 47	n = 47	n = 55	n = 54
	18.1	13.1	16.4	23.1
At 6 courses	n = 40	n = 37	n = 41	n = 38
	17.6	13.0	16.1	23.3

Each theoretical schedule was feasible as by Mann-Whitney tests, the distributions of the relative intensities were not statistically different. Comparisons of response rates at 3 courses and of overall survival curves by treatment arm were not statistically different in the 2 series of pts and remained not significant when stratified by relative global dose intensity. However, in responders to the induction CT, using a Cox model, administration of a maintenance CT as well as an increased ADI of the anthracyclin drug -with the equivalence of 60 mg epirubicin to 45 mg

adriamycin- ($P = 0.03$) had a positive impact on survival in both series of pts suggesting a potential benefit of a prolonged treatment when adjusting for the intensity of the first regimen.

92 POSTER

CPT 11 (IRINOTECAN) IN PRETREATED SMALL CELL LUNG CANCER (SCLC): A PHASE II STUDY IN PATIENTS PROGRESSING AFTER A FIRST RESPONSE (PRELIMINARY RESULTS)

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The standard combination chemotherapy of SCLC is an etoposide based regimen. After failure of this regimen the prognosis is very poor although the use of a rescue regimen still displays clinical activity.

It has been already suggested that investigational new drugs should to be assessed in second line therapy in SCLC and that a RR $\geqslant$ 10% among 29 patients would be relevant for the screening of active new compounds.

CPT11 is a new DNA topoisomerase I inhibitor active in colorectal cancer and other solid adult tumors.

22 patients with progressive extensive SCLC after a prior response on a VP16-based chemotherapy have been so far entered onto the study. Sex ratio M/F =19/3; median age = 57.2 (43–72). Performance Status 0 = 14%; 1 = 45%; 2 = 41%. Median number of involved organ 4 (1–6) with liver (27%), lung (22%), lymph nodes (16%) and brain (11% of patients).

57 cycles at the planned dose of 350 mg/m^2 every 3 weeks have been delivered with a median Relative Dose Intensity of 0.95 (0.78–1.03).

Efficacy: One CR and three PR have been observed among the 15 evaluable patients.

Safety: The incidence of grade 3 and 4 toxicity per cycle has been: neutropenia: 49% (with febrile neutropenia sepsis in 14%), delayed diarrhea: 18%, nausea vomiting: 14%.

Conclusion: The activity of CPT 11 in SCLC is likely to be attractive on the basis of these preliminary data. Neutropenia is clearly the dose limiting toxicity in this population of pretreated patients with frequent occult bone marrow involvement.

93 POSTER

A NEW STAGING SYSTEM FOR SMALL CELL LUNG CANCER (SCLC): A PROPOSAL

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The staging system should aim at four goals: (1) to define more accurate prognosis for individual pts; (2) to help in treatment planning in clinical practice; (3) to better compare therapeutic results in clinical trials; and (4) to define optimal risk groups for pt stratification in prospective studies.

From 2/85 to 6/93, 173 consecutive pts with SCLC received treatment tailored to disease extent. Fourteen out of 16 pts with stage I and II, 25/62 with stage IIIA and 5/37 with stage IIIB were subjected to surgery plus chemotherapy (CT) and RT (chest and brain). Pts with inoperable stage I–II (2/16) and III (IIIA 37/62, IIIB 32/37) received CT followed by RT while CT +/− symptomatic RT was administered in pts with stage IV disease. In all pts CT consisted of CAV-like regimens and/or cisplatin + VP16. The 5-year results (%) are as follows:

		Extent		Stage				
	Total	Limited	Extended	I	II	IIIA	IIIB	IV
FFP	16	24	0	54	50	22	15	0
Survival	16	26	0	67	65	19	27	0

Our data confirm the prognostic value of limited vs extended SCLC. However, analyzing our data according to a different stage grouping we obtained the following results:

New stage grouping	Stage (TNM)	% FFP (5-yrs)	% Survival (5-yrs)
Limited (L)	I–II–IIIA (T3N0)	48*	49**
Locally-extended (LE)	IIIA (T3N1–2)-IIIB	19*	22**
Extended (E)	IV	0*	0**

*L vs LE $P = 0.007$ *L vs E $P = 0.0001$ *LE vs E $P = 0.0001$ **L vs LE $P = 0.0025$ **L vs E $P = 0.0001$ **LE vs E $P = 0.0001$

This 3-stage grouping seems to better correlate with long-term results and may represent a more reliable staging model for SCLC.

94 PUBLICATION

SMALL CELL LUNG CANCER (SCLC) AND LONG-SURVIVORS. A REVIEW OF 276 PATIENTS (P)

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We reviewed 276 patients (pt) with histologically confirmed SCLC in a single institution from January 1981 to May 1992. They were treated with three different combination chemotherapy regimens. Among 251 evaluable patients only 18 (7.17%) were alive after two years (y). All these patients were men with a median age of 59 y. All but four had Limited Disease (LD). Four patients were treated with ECCP regimen (VP-16, CYC, CcNU, prednisolone), 4 with ECCA (VP-16, CYC, CcNU, ADM) and 10 with ECAP (VP-16, CYC, ADM, PCB). Among the 18 pt, 5 pt underwent chest radiotherapy and also 5 underwent prophylactic brain irradiation. Fifteen pt got a complete response (CR) and the time diagnosis-treatment was brief with a median time of 3.3 days. All the 18 pt had 0–1 ECOG performance status (PS) and most of them (15/18) a PS = 0. The 4 pt with Extensive Disease (ED) had disease in contralateral axila (1), bone and liver (1) and 2 pt were classified as ED because of exclusively having mediastinal syndrome. The median survival was 51 months (26–89 m) and, in May 1994, 9 pt were alive, 8 had died and 1 had disappeared on follow-up. Seven pt lived more than 5 y (2.78%). This results confirm that stage (LD), high PS and getting a CR are the main prognostic factors and, although relapses may exist after 2 y of survival, two-thirds of the patients being then free of disease will not relapse in the future. To find new drugs with more cytotoxic power is mandatory.

95 PUBLICATION

FOUR VERSUS 6 COURSES CISPLATIN ETOPOSIDE (E.P.) WITH EARLY CHEST RADIOTHERAPY. A RANDOMIZED STUDY IN SMALL CELL LUNG CANCER (SCLC)

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Despite several trials testing increased dose intensity, alternating drug administration etc. the survival of patients (pts) with SCLC has not improved. Early chest radiotherapy in pts with Limited Disease (LD) has been shown to improve patients' survival. In an effort to reduce toxicity we have compared the efficacy and toxicity of 4 courses (Group A) versus 6 courses (Group B) of EP chemotherapy combined with early chest radiotherapy. In a randomized study 52 evaluable pts have been treated with E.P. (Etoposide 120 mg/m^2 days 1–3, Cisplatin 80 mg/m^2 day I). All responders have been irradiated after the 4th course. Objective Response (O.R.) for Group A was 16/24 = 66%, with 5 CRS 20% and 11 PRS 46%, Group B OR: 21/28 = 75% with 7 CRS 25% and 14 PRS 50%. Median Time to progression group A: 8 mo group B: 13 mo ($P = 0.050$) Median Survival group A: 9 mo (5–28+) group B: 12.5 mo (6–43+) ($P = 0.033$). Median Survival LD pts group A: 15.6 mo, Group B: 20.5 mo (N.S.). Extensive Disease (E.D.) Group A: 7.5 mo, Group B: 11.5 mo ($P = 0.027$). Myelotoxicity and renal toxicity were not significantly different. We consider 4 courses inferior to 6 courses even with early radiotherapy. E.D. patients seem to benefit more from the two extra courses.

96 PUBLICATION

NONESOPHAGICAL EXTRAPULMONARY SMALL CELL CARCINOMA

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Extrapulmonary small cell carcinoma (ESCC) is a well known but uncommon neoplasm of uncertain origin. In spite of its rarity, the appearance of this type of tumor has been described in various organs of the economy. Of these, the esophagus has usually been reported as the most common location.

Eight patients with nonesophagical small cell carcinomas have been evaluated in our service between 1988–1995, constituting 2.2% of all small cell carcinoma (SCCs) that we have seen in the same lapse of time.