toxicity (WHO G3 + 4) for arm A: leucopoenia 90% vs 75%, thrombocytopoenia 37% vs 19%, blood transfusions 59% vs 48%, infectious episodes 58% vs 48%. Oesophagitis (4%) and late lung toxicity (38%) were similar in A and S. Median survival was 15 month and combined response rate (CR + PR) 69% in A and 84% in S ($P = 0.012$). Using predefined criteria 36% A and 30% S patients needed dose reductions and 29% A, 27% S treatment delays with 20% A and 9% S not completing the planned 5 courses of chemotherapy.

The results of this unique trial will help to identify the role of alternating treatment schedules in good prognosis SCLC.

78 ORAL

DOSE INTENSIVE CHEMOTHERAPY IN PATIENTS WITH ADVANCED SMALL CELL LUNG CANCER (SCLC): PRELIMINARY RESULTS OF A MULTICENTER RANDOMIZED TRIAL

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A 25%–33% increase in initial doses of cisplatin (CDDP) and cyclophosphamide (CPM), when combined with standard doses of doxorubicin and etoposide, has been found sufficient to significantly improve both disease free and overall survival in patients with limited SCLC (*NEJM* 1993, **329**, 1148–1152). In this following trial, we are testing whether or not an increase in dose-intensity of a quite similar 4-drug regimen leads to an improvement in survival. From October 1991 to December 1994, 123 patients with untreated SCLC were enrolled in this study comparing "standard dose" (SD) PEVEP for 6 cycles versus " high dose " (HD) PEVEP + rh-GMCSF (E. Coli derived) for 4 cycles. SD PEVEP consisted of: Epirubicin 40 mg/m^2 dl, CDDP 100 mg/m^2 d2, Etoposide 75 mg/m^2/d dl-3, CPM 400 mg/m^2/d dl-3. In the HD PEVEP arm the intended doses for each cycle were increased by 50% except for CDDP: 25%. This HD PEVEP arm was supported by a systematic use of rh-GMCSF (5 μg/hg/d s. c.) administered from d4 to d13. Thus, the cumulative doses in both arms were roughly similar. Responding patients with residual disease confined to the chest were eligible for thoracic radiation. Complete responders were eligible for prophylactic cranial radiation. An interim analysis was performed as planned by the protocol after the inclusion of 50% of 200 patients required to demonstrate a 50% improvement in median survival. Accrual has been closed prematurely on 12/23/94 due to a significant survival difference between the two arms. An updated analysis will be presented.

79 ORAL

A RANDOMIZED STUDY OF INITIAL VS DELAYED CHEST IRRADIATION WITH CHEMOTHERAPY IN LIMITED STAGE SMALL CELL LUNG CANCER

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The timing of chest irradiation (CI) with respect to combination chemotherapy (CT) may influence the probability of resistant tumor cell dissemination in limited stage small cell lung cancer. Therefore, a randomized study was undertaken comparing initial CI (ICI) (99 patients) with "late" (18 weeks delayed) CI (LCI) (100 patients). All 199 eligible patients received cisplatin and etoposid alternating with cyclophosphamide, doxorubicin and vincristine at intervals of 3 weeks. CI was given in 22 fractions as a split course with cisplatin and etoposid in the interval. The central dose was originally 40 Gy, later increased to 45 Gy. Total duration of CI + CT was 7 mo. The total dose of CI and CT actually given in the two groups was similar. Median age was 60 (36–70) yrs. Minimum follow-up was 5 years. None of the endpoints studied differed significantly between LCI/ICI: treatment toxicity, local response (CR = 61/59%), median survival (366/320 days), 2-yr survival (18.0 ± 3.8/20.2 ± 4.0 (± SE) %), and 5-yr survival (10.8 ± 3.1/10.8 ± 3.1%). The estimated ratio of hazard rates was 0.88 with 95% conf. lim. [0.66, 1.18]. Taking a 5-yr survival of 11% after ICI as the reference, the estimated 95% conf. lim. for the 5-yr survival after LCI are 7% and 23%. Thus the current trial shows that the benefit, if any, from a changed timing of CI relative to CT can only be relatively modest.

80 ORAL

DOSE-INTENSIFICATION OF V-ICE CHEMOTHERAPY WITH GM-CSF IN SMALL CELL LUNG CANCER (SCLC)—A PROSPECTIVE RANDOMISED STUDY OF 301 PATIENTS

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Patients (pts) with SCLC and ≤ 3 adverse prognostic features (Manchester system) were randomised in a multicentre prospective study to 6 courses of VICE chemotherapy (ifosfamide 5 g/m^2, carboplatin 300 mg/m^2, etoposide 120 mg/m^2 iv d1, 2 & 240 mg/m^2 po d3, vincristine 0.5 mg/m^2 d14) every 3 or 4 weeks ("intensified" & "standard" arms respectively). Pts received 14 days of granulocyte-macrophage colony-stimulating factor (GM-CSF) or placebo (250 μg/m^2/d) between each course in a double-blind fashion. Endpoints are to determine the effects of dose-intensity and GM-CSF on outcome.

301 pts were entered from 17 centres in Europe (70% from 4 centres) up to 1/94. Sixty-three percent had ≤ 1 adverse prognostic feature and 41% had extensive stage disease (similar distribution in "fixed" and "intensive" arms). Overall, 30% greater dose-intensity was administered to pts in the "intensive" arm. Preliminary outcome assessments are: "fixed" arm—documented sepsis—28 pts, OR 76% (52% CR), 8-month survival 63%; "intensive" arm—documented sepsis—11 pts, OR 87% (47% CR), 8-month survival 75%. Detailed outcome analysis with assessment of the effects of GM-CSF will be performed in 6/95 with a minimum follow up of 1 year.

81 ORAL

MAINTENANCE CHEMOTHERAPY IN PATIENTS WITH SMALL CELL LUNG CANCER AFTER INDUCTION CHEMOTHERAPY WITH IFOSFAMIDE, ETOPOSIDE AND ANTHRACYCLIN: RANDOMIZED TRIAL CONDUCTED BY THE EUROPEAN LUNG CANCER WORKING PARTY

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Our group has conducted in previously untreated patients with small cell lung cancer a randomized trial (closed in May 1993) having as primary endpoint the effect on survival of a maintenance chemotherapy (etoposide 120 mg/m^2 d 1–3 + vindesine 3 mg/m^2 d 1, every 3 weeks, 12 courses) given to responding patients after 6 courses of induction chemotherapy. As secondary endpoint, there was a comparison between adriamycin (45 mg/m^2) (IV A) and epirubicin (60 mg/m^2) (IVE60) in one set of patients and between two dosages (60 vs 90 mg/m^2) (IVE60 vs IVE90) of epirubicin in a second set, in combination with ifosfamide and etoposide. Six courses were given at 3 to 4 weeks intervals. On 235 patients eligible for induction therapy, after the 6 courses, 91 were randomized between maintenance (M) (45 pts) and no maintenance (noM) (46 pts). At time of analysis, median follow-up was 175 (range 98–241) weeks after registration and 155 (range 74–219) weeks after randomisation and 77 patients died. Median survival time was 38 weeks (95% CI 27–43) for noM and 48 weeks (95% CI 33–55) for M ($P = 0.10$, logrank test). In univariate analysis, good Karnofsky PS and limited disease were good prognostic factors. In multivariate analysis, only disease extent was a significant prognostic factor. We concluded that maintenance chemotherapy resulted in a statistically non significant survival improvement.

82 ORAL

TREATMENT OF SMALL CELL LUNG CANCER (SCLC) IN ELDERLY PATIENTS (E.P.)

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Aim: to analyze the treatment outcome for E.P. (i.e. older than 70 yrs) affected by SCLC treated at our institution with the same protocol and entry criteria as younger pts. *Results:* From 1980 to 1988, 286 patients (M/F: 262/24) were treated; 254 (88%) were younger than 70 (Y.P.) while 32 (12%) were E.P., Pt. characteristics were similar in both age groups: median PS was 80% vs 80%, increased LDH 46% vs 47%, weight loss 55% vs 53%, limited disease (LD) stage 58% vs 56%. stages I–II 18% vs 18%, IIIA 26% vs 31%, IIIB 17.3% vs 15.6%,

IV 38.2% vs 34.4%, operable pts 35% vs 31% respectively in Y.P. and E.P. Surgery, however, was performed in 73 (28.7%) Y.P. and in only 6 (18.8%) E.P.. Chemotherapy (CT) consisted of 6 courses of alternating CAV/PE for extensive disease pts.. LD pts were treated with 4 cycles of CT plus surgery in operable pts; RT (44 Gy) followed CT in inoperable pts. Two pts had an early death before starting treatment, 3 pts were submitted only to surgery for refusal of CT, all in Y.P. group. In 44 pts surgery was followed by adjuvant CT. A total of 237 pts were submitted to primary CT, 210 pts were Y.P., 27 E.P.: objective response rates were 72% and 63% respectively, with 26.7% (56 pts.) and 22.2% (6 pts.) CR. Median survival was 11.6 and 12 months and 3 yrs survivals were 18% and 17.8%. Cox proportional hazard survival analysis showed no significant differences by age. *Conclusions:* compliance, responses and survival were similar in Y.P. and E.P. treated for SCLC. Thus an aggressive therapeutical approach seems to be justified in selected patients older than 70 yrs.

83 ORAL

PROPHYLACTIC CRANIAL IRRADIATION (PCI) FOR PATIENTS (PTS) WITH SMALL CELL LUNG CANCER (SCLC) IN COMPLETE REMISSION (CR)

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Two randomized trials were planned to evaluate the effect of PCI (24 Gy/8 fractions/12 days) on brain metastasis (brmet), overall survival (OS) and late toxicity rates in pts. with SCLC in CR. The first trial (PCI85) included 294 evaluable pts. and showed that PCI decreased the risk of brmet 3-fold without a significant increase in complications. A possible beneficial effect on overall survival was not statistically significant ($P = 0.14$). The second trial (PCI88) was started in 1988 with a simplified schedule to increase pt accrual and the statistical power so that a potentially beneficial effect on overall survival would be detected. This trial included 211 pts and was closed in April 1994. In the two trials, 505 pts. are evaluable, 418 with limited disease and the median follow-up was 63 months. Only one pt. was lost to follow-up. Overall results are summarized as follows:

	2-year rates				
Endpoint	PCI(+)	PCI(−)	RR	(IC)	p Value
Overall brmet	40%	59%	0.45	(0.34–0.60)	$<10^{-4}$
Isolated brmet	39%	57%	0.41	(0.30–0.57)	$<10^{-4}$
OS	31%	27%	0.85	(0.69–1.03)	0.10

In conclusion, the effect of PCI on overall survival in pts with SCLC in CR was not statistically significant. A meta-analysis of similar trials should be conducted to evaluate a possible beneficial effect of PCI.

84 ORAL

PHASE II STUDY OF TOPOTECAN IN REFRACTORY AND SENSITIVE SMALL CELL LUNG CANCER (SCLC)

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Topotecan (T) is a semisynthetic-camptothecin analog with specific topoisomerase I inhibitory effect and preclinical activity in a broad range of tumors including SCLC. A multicentre Phase II study to assess activity and toxicity in pretreated SCLC patients (pts) has recently been closed. Two groups of pts were enrolled: "sensitive" (S) pts who responded to 1st line chemotherapy (CT) but progressed <3 months afterwards and "refractory" (R) pts who never responded to 1st line CT or progressed <3 months after 1st line CT. T was administered iv at a dose of 1.5 mg/m^2 d×5 q3 weeks until progression or excessive toxicity. A total of 94 eligible pts were entered and 353 courses (crs) and 87 pts (48 R, 39 S) have been evaluated. Pts characteristics are: median age 59, median PS 1, median duration of prior CT 4 months and median No. of prior drugs 3. In 39 S pts 5 CR and 13 PR were observed (46%), in 48 R pts 1 CR and 3 PR (8%). Toxicity (NCI grading) was mainly hematological. Leucopenia, although short-lived was common with gr. III and IV neutropenia occurring in 78% of crs. Nine pts developed infections, 2 died while neutropenic. Gr. III and IV thrombocytopenia was observed in 29% of crs and 54% of pts. Anemia gr. III and IV occurred in 29% of pts. Non-hematological toxicity was mild. Asthenia was observed in 35% of crs with only 3 gr. IV episodes. Diarrhea was reported in 12 crs (1 gr. III), vomiting gr. III in only 1 crs. Toxicity required dose reduction in 10% of courses, treatment delay in 18% of crs. Preliminary results indicate that the concept of testing new drugs in S and R pts is feasible, that T has significant activity, especially in S, but even in R pts, and that toxicity is manageable. The study is closed for patient entry and final results will be available in October 1995.

85 POSTER

A PROSPECTIVE RANDOMISED STUDY IN LIMITED DISEASE SMALL CELL CARCINOMA—DOXORUBICIN AND VINCRISTINE PLUS EITHER CYCLOPHOSPHAMIDE OR ETOPOSIDE

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A prospective randomised study was undertaken in patients with limited disease small cell carcinoma of the lung between March 1990 and August 1993. Doxorubicin, 50 mg/m^2, and vincristine, 2 mg iv on day 1 was given with either cyclophosphamide, 800 mg/m^2 (CAV) or etoposide, 60 mg/m^2 iv on day 1 and 120 mg/m^2 orally on day 2 to 5 (AVE). Responding patients were to receive 6 cycles of chemotherapy at 3-weekly intervals followed after 2 weeks by mediastinal irradiation.

	CAV	AVE	
Patients	38	43	
Complete response rate	32%	51%	($P = .07$)
Partial response rate	29%	23%	
Median survival	12 mo.	14.5 mo.	($P = .15$)
Leukopenia Grade 3	18%	7%	
Grade 4	11%	2%	($P = .03$)
Paraesthesiae	24%	23%	

No patients developed doxorubicin cardiomyopathy. This confirms the role of etoposide in first line chemotherapy for SCCL. Its use in combination with doxorubicin may be preferable to its use with cyclophosphamide in view of the low toxicity and efficacy observed.

86 POSTER

PRELIMINARY RESULTS OF A STAGE ORIENTATED MULTIMODALITY TREATMENT INCLUDING SURGERY FOR SELECTED SUBGROUPS OF LIMITED DISEASE SMALL CELL LUNG CANCER (SCLC)

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Since 6/91, 38 patients (pts) with limited disease SCLC (mediastinoscopy obligatory) have been entered into this ongoing trial. Pts with stage I and II were treated with 4 cycles cisplatin (50 mg/m^2 d 1 + 7) and etoposide (170 mg/m^2 d 3, 4, 5) = PE, q d 22 followed by restaging and surgery. IIIa pts were treated with 3 cycles of PE, q d 22 followed by one cycle simultaneous RTx/CTx (45 Gy, 1, 5 Gy twice daily within 3 weeks; P 50 mg/m d 2 + 9 of RTx, E 100 mg/m^2 d 4, 5, 6 of RTx) followed by remediastinoscopy and operation. IIIb pts were treated with 4 cycles PE, q d 22 followed by sequential RTx or 3 cycles PE plus 1 cycle of PE with simultaneous RTx (50 Gy, conventional fractionation, 2 Gy daily for 5 weeks). *Pts characteristics:* m/f 26/12; age 55 (34–69); PS 1 (0–1); Stage I 6, II2, IIIa 17, IIIb 13. *Results:* after CTx +/− RTx cCR 14; PR 21, CR/PR 35 (92%), MR 2. TOXICITY (WHO): lucopenia 3° 25%, 4° 10%; Infection 3 ° 10%, 4 ° 5%; thrombocytopenia 3°/4° 20%; diarrhea 3° 5%. One pt died of treatment related septicemia. Seventeen out of 25 (68% (stage I 6/6; stage II 2/2; stage IIIA 9/17)) pts underwent R0 resection including 7 (28%) pCR's. So far CNS relapses were the only site of failure in 7/17 pts who had R0 resection. None of them failed locoregionally. The median observation time for pts alive is 15 (3–46) months (mts). The median survival for all 38 pts is 29 (3+–46+) mts; stage I–IIIA not yet reached (3+–46+ mts), and R0 resection not yet reached (5+–46+ mts, 71% at 27 mts); stage IIIB 15 (6+–35+)mts. *Conclusions:* This intensive stage oriented multimodailty program is tolerable and highly effective for LD SCLC. Of note is the high local tumor control rate (100%) of pts with stage I–IIIA who underwent R0 resection.