all 6 cycles at the prescribed dose, but 69% strictly respected intercycle intervals.

Mild digestive and cutaneous toxicity (grade 1 and 2) was observed in 50%. Major toxicity was neutropenia (grade 2 or 3) in 18 patients and 1 severe infection. The 3 year actuarial survival rate was 87%. No local relapse was observed. Metastases occurred in 6 patients.

These preliminary results show that this concomitant association is safe although compliance to chemotherapy should be improved.

74 PUBLICATION

CONCOMITANT ADJUVANT CHEMOTHERAPY (FNC REGIMEN) AND RADIOTHERAPY IN OPERABLE STAGE II BREAST CANCER (O.B.C.)

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The purpose of multimodality treatment including simultaneous radiochemotherapy is to reduce the total length of the adjuvant treatment after surgery. Aims of study were to evaluate the compliance, global toxicity and local cutaneous side effect. The treatment scheme is F.N.C (F: Flourouracil 500 mg/m^2, N: Mitoxantrone 12 mg/m^2, C: Cyclophosphamide: 500 mg/m^2) every 21 days. Six cycles for N+, 4 cycles for N− with poor prognosis (RH- or SBR III). Radiotherpy is indicated by the consensus of the "Societe Française de Radiotherapie Oncologique" S.F.R.O. (50 Gy/25 fractions/5 weeks, 15 Gy overdose when T > 10 mm).

We report a feasibility study in 154 pts with O.B.C. included from May 90 to October 95 Median age: 49, 5 y (29–72), postmenopausal: 46.8%; premenopausal: 52.6%; Performance Status O: 96.7%, 1: 2%, unknown: 1.3%, Radical surgery: 29.9% conservative: 69.5%, N−: 29.9%; N+: 70.1%. Ductal carcinoma: 85.7%, lobular: 5.8%, SBR I: 2.6%, SBR II: 26.6%, SBR III: 65.6%.

Total number of courses was 773 (60.4% of pts received 6 courses). Full dose of N was administered to 84.4% of pts, F to 90.3%, C to 88.3%. Interval between 2 cycles was 21 days in 30.9% pts, 28 days in 45.4% pts, upper than 28 days in 23.7% pts. Median total radiotherapy dose was 50 Gy. Main toxicities observed (per pts) were: gastrointestinal grade 3–4: 4.6%, dysphagia: 27.9%, leucopenia grade 3–4: 12.3%, anemia grade 2: 2%, thrombocytopenia grade 2: 1 pt. A reversible cardiotoxicity occurred in 15 pts including extrasystole: 1 pts, low blood pressure: 2 pts, pericarditis 3 pts. Local toxicity was mild (grade ⩽ 1: 62.3%, grade 2: 16.9% and grade 3: 4.5%). No major pulmonary toxicity was observed. Quality of life (E.C.O.G scale) was performed to evaluate the repercussion of this treatment grade 0: 44.2%, grade 1: 34.4%, grade 2: 7.8% and grade 3 in 1 pt. Well acceptability of treatment in 51.9% of pts.

Mitoxantrone containing chemotherapy and postoperative radiotherapy can thus be combined in an adjuvant treatment program with good compliance and acceptable toxicity. Ongoing or further study of a large patients groups comparing various strategies of chemotherapy and radiation sequencing will be needed to confirm our data.

75 PUBLICATION

A PILOT STUDY OF ADJUVANT POSTOPERATIVE CHEMOHORMONAL THERAPY WITH 5-FLUOROURACIL, DOXORUBICIN, CYCLOPHOSPHAMIDE, VINDESINE AND TAMOXIFEN FOR RESECTABLE BREAST CANCER

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Adjuvant systemic therapies have proved effective to increase disease-free survival (DFS) and total survival at 5 and 10 years in patients with "resectable" breast cancer. However, the amount of the benefit is at best moderate. There is a need of more effective regimens.

We show the results of a pilot trial of postoperative adjuvant therapy with 6 cycles of 5-Fluorouracil 600 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 600 mg/m^2 and vindesine 3 mg/m^2 (maximum 5 mg), all endovenous on day 1, repeated every 28 days, plus Tamoxifen (20 mg/day) continued for 2 years (not in ER negative tumors). This schedule of chemohormonotherapy had been demonstrated highly active in metastatic breast cancer. Three-hundred and five patients (pts) have been treated. Menopausal status was: premenopausal in 93 pts and postmenopausal in 212. ER status was (+) in 90 pts, (−) in 61 pts and unknown in 154 pts. Twenty-three pts had node negative stage II tumors with peripheral blood or lymph vessel invasion (PBLI), 75 pts had 1 to 3 positive nodes, 33 pts had 4 to 10 positive nodes, 15 pts had 10 or more positive nodes and 159 pts had technically respectable stage III tumors +/− axillary nodes (N0, N1 o N2). (stage IIIA 87 pts and stage IIIB 72 pts). More than 90% of the patients received 6 cycles of chemotherapy at full dose. Median follow-up is now 44 months (80 pts followed for 5 years or longer). Actuarial 5 year DFS is 84% for N(−) stage II with PBLI; 79% for pts with stage II (1–3 nodes); 70% for pts stage II (3–10 nodes); 62% for stage II (>10 nodes) and 56% for stage III. DFS and total survival according to menopausal status and ER status will be presented.

We feel that such stimulating results in this uncontrolled pilot trial deserve testing in a randomized multi-institutional study.

76 PUBLICATION

ADJUVANT FOUR CYCLES OF EPIRUBICIN AND CYCLOPHOSPHAMIDE WITH RADIATION THERAPY IN OPERATED STAGE II–III BREAST CANCER

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Between April 1992 and March 1993, 96 operated patients with stage II–III breast cancer received adjuvant treatment consisting of Epirubicin (70 mg/sqm) and Cyclophosphamide (600 mg/sqm) I.V. every three weeks for 4 cycles and followed by locoregional radiation therapy. Median age was 41 (range 25–60). Sixty-eight patients were in stage II, 28 in stage III. Seventy-nine we premenopausal and 17 postmenopausal. WHO Grade 2–3 side effects were: Leucopenia 18%, and alopecia 60%. Cardioxicity was not observed.

After a median follow-up of 28 months, 18 patients presented recurrences (3 local and 15 distant) five patients died during the follow-up. Adjuvant combined 4 cycles of EC followed by radiation therapy is an affective treatment with high local and distant control, and shortens the treatment time in stage II–III operated breast cancer.

Small cell lung cancer

77 ORAL

RANDOMISED COMPARISON OF ALTERNATING OR SEQUENTIAL SCHEDULES OF CHEMORADIOTHERAPY IN LIMITED SMALL CELL LUNG CANCER (SCLC) TRIAL OF THE EORTC LCCG(08877)

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Combined modality therapy is becoming standard treatment for "good prognosis" patients with SCLC but the optimal schedule and timing of thoracic irradiation is as yet unclear.

The EORTC LCCG has completed a randomised comparison of alternating (A) vs sequential (S) schedules of CDE chemotherapy and thoracic irradiation (50 Gy in 20 fractions) with identical total chemotherapy and radiation doses and overall treatment time; the schedule as the only variable. This trial will close on 31.3.1995. Three hundred and forty-nine patients have been randomised (174 in A, 175 in S), 11 were inelligible. Mean age was 60, M/F = 2/1, PS 0 (46%), 1 (47%), 2 (5%) and 3 (2%). Weight loss was < 10% in 76%. All these parameters are similar in both arms. First full analysis will be performed 6 months following trial closure and will be presented. Interim analysis performed on 285 patients (144 A and 141 S) showed consistently higher rates of

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%,