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A PHASE II TRIAL OF INDUCTION CHEMOTHERAPY FOLLOWED BY INTENSIFICATION WITH HIGH-DOSE (H.D.) CHEMOTHERAPY OR CONCURRENT CHEMO-RADIOTHERAPY AND RECOMBINANT G-CSF IN EXTENSIVE (E.D.) AND LIMITED (L.D.) SMALL CELL LUNG CANCER (SCLC).

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From November 1991 to November 1992, 36 patients (pts) with SCLC (median age 61, L.D. 17, E.D. 19) received induction chemotherapy with Cytoxan (1 gr/sqm day 1), Epirubicin (90 mg/sqm day 1), Vincristine (2 mg day 1) (CEV) q 3 wks for 2-3 courses. 32 pts are evaluable for response to CEV: in L.D. we obtained 12/14 P.R. + C.R. (86%) - 4 C.R. (28%). In E.D. we obtained 13/18 P.R. (72.2%). Of 25 responsive pts (78,1%), 22 (11 L.D. and 11 E.D.) received, at this moment, intensification consisting of H.D. chemotherapy: Carboplatin (150 mg/sqm days 1-2-3) , VP16 (100 mg/sqm days 1-2-3-4-5) plus rhG-CSF 5 mcg/kg/die from day 7 to day 16 q 3 wks, for three courses. In LD, 11 pts received concurrent radiotherapy in two daily fractions on tumor volume (45 Gy), starting with H.D. chemotherapy. With H.D. chemotherapy 4 P.R. was transformed in C.R. and the entity of response in 6 pts with P.R. was substantially improved. Myelosuppression was the main side effect of intensified treatment: there were 16 episodes of Grade III-IV neutropenia and thrombocytopenia over 63 courses of HD chemotherapy. Grade IV thrombocytopenia was present in 6/11 pts treated with concurrent chemo-radiotherapy and in two cases required platelet transfusions. However, the nadir of myelo-suppression lasted only a few days (2-3) and treatment was ambulatorial and very well tolerated. No toxic deaths have been reported. Our data indicate that intensification of treatment with G-CSF support is feasible and can increase response rate in pts responding to induction chemotherapy.

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WEEKLY CARBOPLATIN (CARBO) PLUS CHRONIC ORAL ETOPOSIDE (VP-16) AS FIRST LINE THERAPY IN SMALL CELL LUNG CANCER (SCLC). A PHASE II TRIAL.

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From June 1990 to October 1992, twenty-seven consecutive untreated patients (pts) diagnosed of SCLC (limited disease (LD) 19 pts and extensive disease (ED) 8 pts), received 3 courses of CARBO 150 mg/m2 e.v. days 1-8-15 and VP-16 50 mgr/m2/day p.o for 21 succesive days every 4 weeks. Six complete responses (22%) and 15 (55%) partial responses were achieved. Overall responses rate of 77% (95% confidence interval 67% - 87%). Median survival was 10.5 months (15.3 in LD and 8.5 in ED). Alopecia excepted (92% of pts), non hematologic toxicity was mild. Hematological toxicity (WHO grade) II + III consisted in anaemia, 17%; leukopenia, 34%; granulocytopenia, 28%; thrombocytopenia, 5%. Grade IV of leukopenia and granulocytopenia were observed in two pts. There were no toxic related deaths. Two pts were admited into the hospital because of fever and granulocytopenia.

Chronic oral VP-16 plus CARBO weekly is well tolerated and appears to be active in SCLC. Continous infusion of both drugs is now under clinical research.

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CARBOPLATIN (Ca) AND ORAL ETOPOSIDE (E) IN PREVIOUSLY UNTREATED PATIENTS WITH SMALL CELL LUNG CANCER.

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From March 1988 to June 1992, 106 (LD/ED; 44/62) previously untreated and consecutive patients with SCLC were treated with an out-patient regimen of Ca 300 mg/m² IV on day 1 and E 240 mg/m² orally days 1+2+3 every 4 weeks for 6 cycles. Median age was 59 years, median PS was 1 (range, 0 to 4). Thoracic irradiation (45.00 Gy/22 fractions) was given as split course therapy to responding patients with LD. Objective response was seen in 89% (CR/PR; 44/45) of pts with LD and in 52% (CR/PR; 6/46) with ED. Median survival for patients with LD, ED and all patients was 14.5 months, 8 months and 10.5 months, respectively.
93% (LD) and 58% (ED) completed 6 courses of CaE. For various reasons part of etoposide was administered IV in 31%. Leucopenia and trombocytopenia WHO grade III-IV was observed in 22% and 17%, respectively. One patient died of sepsis during leucopenia. Nausea/vomiting was mild. Alopecia requiring a wig occured in all patients. No neurotoxicity, nephrotoxicity, or ototoxicity was observed.
CaE is an effective and manageable outpatient-regimen with mild toxicity.

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CARBOPLATIN PLUS EPIRUBICIN PLUS VP-16, CONCURRENT RADIOTHERAPY AND "ADJUVANT SURGERY" FOR LIMITED SMALL CELL LUNG CANCER (SCLC).

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Thirty-four patients (pts) with limited SCLC were subjected to CEV chemotherapy (carboplatin 300 mg/sqm, i.v., d 1; epirubicin 50 mg/sqm, i.v., d 1; VP-16 100 mg/sqm, i.v., d 1-2-3, every 4 weeks), and concurrent "split course" radiotherapy (4000 cGy, in course of 2000 cGy, weeks 6-7 and 10-11) followed by surgery for pts achieving CR or PR. Pts were excluded from surgery if staged T4-N3 at diagnosis. In 32 evaluable pts after induction therapy we obtained 93,7% OR with 62,1% CR. Median duration of response was 12,5 months for PR and 10 months for CR. Nine pts were elegible for surgery after induction therapy. Five pts were subjected to surgery (4 CR with 3 pathological confirmation and 1 PR unresectable); 4 refused. Median survival for all pts was 14 months with 9,3% long-term survivors at 36 months. Toxicity consisted mainly of myelosuppression. These preliminary data show high activity of CEV chemotherapy and chemo-radiotherapeutic regimen employed. The role of "adjuvant surgery" in stage III A is being evaluated.

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PHASE I STUDY OF CARBOPLATIN, EPIRUBICIN AND VP-16 PLUS G-CSF IN EXTENSIVE SMALL CELL LUNG CANCER (SCLC).

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Carboplatin (300 mg/sqm, i.v., d 1), epirubicin (50 mg/sqm, i.v., d 1) and VP-16 (100 mg/sqm, i.v., d 1-2-3) chemotherapy has shown high activity in SCLC (Gridelli et al., Proc ASCO 11:301, 1992). A phase I study was planned to determine the maximum tolerated dose (MTD) of VP-16 in patients (pts) with extensive SCLC in association with carboplatin (300 mg/sqm, i.v., d 1) and epirubicin (75 mg/sqm, i.v., d 1) with G-CSF support. Fifteen pts received 3 dose levels of VP-16 (mg/sqm, i.v., d 1-2-3): 100 (3 pts), 120 (6 pts) and 140 (6 pts). G-CSF was administered at the dose of 5 mcgr/kg/day, s.c., d 6 to 15. Chemotherapy was recycled every 3 weeks. The MTD of VP-16 was 140 mg and myelotoxicity (leucopenia grade 3 with sepsis in 1 case and thrombocytopenia grade 4 in 1 case) was dose limiting. Overall OR was 92,8%. A phase II study with carboplatin (300 mg/sqm, i.v., d 1), epirubicin (75 mg/sqm, i.v., d 1) and VP-16 (140 mg/sqm, i.v., d 1-2-3) plus G-CSF, recycled every 3 weeks, in extensive SCLC is in progress.