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COMBINED CHEMO AND RADIOTHERAPY FOR SMALL CELL LUNG CANCER (SCLC). LONG TERM SURVIVAL.

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Seventy eight previously untreated patients (pts) with SCLC were treated from September '81 to January '88 with Etoposide 75 mg/m$^2$ d 3-5, Cyclophosphamide 750 mg/m$^2$ IV d 1, Doxorubicin 50 mg/m$^2$ d 1, Vincristine 1.4 mg/m$^2$ IV d 1 and 8. Doxorubicin was increased to 60 and etoposide to 100 mg/m$^2$ for second and third cycles. Courses were repeated every 21 d. All pts received 6 cycles of this combination and were evaluable for response and toxicity. Fifty five pts received CNS prophylactic irradiation. Pts with LS additionally received thoracic radiotherapy. Seventy five pts were male and 3 female. Median age was 54 years (range 34 - 77). 60% of pts had an ECOG performance status 0. Thirty pts had limited stage (LS) and 48 extensive stage (ES) according to the VALCSG criteria.

Sixty three pts (80%) responded to this treatment, 25 with LS (83%) and 38 (79%) with ES. Complete remission (CR) was obtained in 39 pts (50%), 23 (76%) with LS and 16 with ES (33%). The median of duration of CR was 7.5 months for the total group, 11 for the LS and 6 for the ES group. Median survival was 12 months, 15 for LS and 11 for ES . Projected survival at 89 months was 5% for the total group, 15% for LS group and none for ES group (p < 0.01). Toxicity was tolerable but there were 6 toxic deaths. SCLC is a potentially curable disease for patients with limited stage.

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RANDOMISED ADDITION OF THEOPHYLLINE TO CHEMOTHERAPY IN SCLC PATIENTS. A POSSIBLE SYNERGISM.

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Methylxanthines are known to act synergistically with antineoplastic agents in producing DNA damage (Mourelatos D., et al Cancer Research 1988, 48:1129-31). We have also observed synergism of theophyllin with antineoplastic agents when applied to SCLC cell cultures (unpublished data). In order to investigate a possible clinical benefit in SCLC pts, we randomly added an oral slow release theophylline preparation (Choledyl SA) in a dose of 7.5 mg/kg/day, days 1 to 28, in the chemotherapy schedule (carboplatin, ifosfamide and etoposide) of 37 SCLC pts, of whom 22 had limited disease (LD) (group A). This group was compared with 40 pts treated by chemotherapy alone. 27 of them having LD (group B). Overall response rates were not significantly different in the 2 groups (97% vs. 90% respectively). However, CR rates were significantly higher in group A (19/37 vs. 11/40, p<0,05). Hematologic toxicity was higher in group A both for WBCs and plts (p<0,01), therefore strengthening the possibility of synergism. Median survival was comparable in both groups but the data are not final as 20 patients (14 in the theophylline group) are still alive. We conclude that theophylline may be a promising adjunctive therapy in SCLC but further study is needed to define the issue.

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THE SERUM LEVEL OF TUMOR MARKERS (CEA,TPA,NSA,CA19-9) IN SMALL-CELL LUNG CANCER PATIENTS

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It is well known that small cell lung cancer (SCLC) have a great potential for producting multiple endocrine markers. In 24 patients with SCLC the serum level of 4 tumor markers (CEA,TPA,NSE,CA19-9) were analysed before starting the treatment and in monthly intervals after that. The mesured concentrations were compared with the stage of the disease and with the response to the therapy. The mean concentrations of NSE and TPA were significantly greater in the patients with extensive disease than in the limited disease patients (NSE 375 E/ml vs 28 E/ml vs 64 E/ml, p<0,001).The mean level of NSE,TPA,CA19-9 was significantly lower in patients with objective response (CR+PR) than in patients with no response or progres of the disease (p<0,001, p<0,03, p<0,001). Those preliminary results sugest that tumor marker could be used in monitoring of the disease activity, however it still remains to define a role of NSE, TPA and CA19-9 in the predical routine use of benefite to the patients.

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CISPLATINUM (CDDP) AND ETOPOSIDE (VP16) IN "POOR RISK" SMALL CELL LUNG CARCINOMA (SCLCA)

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Fifty patients (pts) with hysto/citological diagnosis of SCLCA were treated with CDDP 30 mg/sm + VP16 120 mg/sm on days 1, 2 and 3 every 3 weeks. The aim of the study was to evaluate the objective remission, the survival and to monitor the quality of life. 8/50 pts had limited disease (LD) and 42 extended disease (ED). The pts with LD had a low performance status (PS) (<50%) and/or concomitant disease, and the pts with ED presented: parenchimal metastases (17), cerebral metastases (5) and more than one metastatic site (16). Forty pts were evaluable for the objective response: 36 males and 4 females, median age 65 (range 42-76), median PS 60% (range 40-80). We observed 2 complete remissions (5%), 26 partial remission (65%), 9 no change (22.5%) and 3 progression (7.5%). The median duration of objective response was 32 weeks (range 9-128) and the median survival was 33 weeks (range 6-128). Side-effects: leukopenia 86%, thrombocytopenia 34% , vomiting 80%, alopecia 97%, diarrhoea 6%. In any case we had to stop the treatment for severe toxicity. We observed an increase of PS in 40% of pts, an increase of body weight in 27.5%, an improvement of at least one symptom (anorexia, cough, hemoptysis, dyspnoea) in 62.5% pts after the treatment. We conclude that fractioned doses of CDDP can improve the tolerance of the treatment and allowed 'poor risk pts" to be submitted to the treatment also as out pts. The percentage of objective responses is comparable to that described in the literature for pts treated with more aggressive regimens. Improvement of subjective parameters (PS and body weight) assure an acceptable quality of life.

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**ANTIEMETIC EFFICACY OF TROPISETRON (TRO) IN PATIENTS WITH SMALL CELL LUNG CANCER (SCLC)**

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51 patients with SCLC (43 men, 8 women, age 58 ± 8.7 years) received TRO as antiemetic prophylaxis in at least one cycle of a chemotherapy consisting of 5 alternating courses of AIO (adriamycin, ifosfamid, vincristin) and PE (cisplatin, etoposide). 209 courses were totally recorded. As regular treatment schedule TRO 5 mg was given once daily i.v. during chemotherapy. In 72 courses the schedule was changed (addition of 5 mg TRO and/or 20 mg dexamethasone).

Results (patients with complete response = no nausea, no emesis):

| course no. | day 1 | day 2 | day 3 | day 4 |
|---|---|---|---|---|
| 1 (AIO) | 31/40 (76%) | 27/40(68 %) | 27/40 (68%) | 23/40 (58%) |
| 2 (PE) | 24/47 (51%) | 22/47 (47%) | 21/47 (45%) | 30/47 (64%) |
| 3 (AIO) | 28/44 (64%) | 25/44 (57%) | 20/44 46%) | 23/44 (52%) |
| 4 (PE) | 23/40 (58%) | 20/40 (50%) | 22/40 (55%) | 26/40 (65%) |
| 5 (AIO) | 26/38 (68%) | 19/38 (50%) | 20/38 (53%) | 21/38 (55%) |

The results demonstrate a good efficacy of TRO in prophylaxis of acute and delayed emesis and nausea sustained over 5 courses of chemotherapy. Incidence of adverse events for course 1 - 5 was maximally 13 %. We conclude that TRO can be recommended for antiemetic prophylaxis in AIO/PE therapy during the whole chemotherapy.

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ORAL ETOPOSIDE, CARBOPLATIN AND VINCRISTINE IN THE TREATMENT OF SMALL-CELL LUNG CANCER.

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From March-90 to April-92 we carried out a chemotherapy treatment on outpatient basis for small-cell lung cancer to assess toxicity, response and survival of a scheme including oral etoposide. Scheme chemotherapy treatment consisted of CARBOPLATIN 325 mg/m2 day 1, VINCRISTINE 1.4 mg/m2 (max.2 mg) days 1, 15 and oral VP 16 50 mg/m2 days 1-21 every 28 days for 6 cycles. As usual locoregional and cranial Radiotherapy was performed for patients with limited disease and CR to chemotherapy. Entry criteria: histologic diagnosis of small-cell lung cancer, no CNS metastasis, age<75 years, performance status<3 (ECOG), no previous treatment.

RESULTS: 30 patients (p) were registered and 24 were evaluable. Median age 61 years (range 41-73). Stage distribution: local disease 11 p (46%), disseminated disease 13p (54%). P. status: PS 0 37,5%, PS 1 54%, PS 2 8,5%. Grades III-IV TOXICITY (WHO): Leukopenia Grade III (16%) Grade IV (25%) ; thrombocitopenia III (12%) IV (12%); Hb III (12%), IV (20%) nausea/vomiting III (12%) IV (8%); peripheral neuropathy III (4%); mucositis III (8%). Six neutropenic fever episodes was registered. Red cell transfusions (8 patients). No toxic deaths has been registered. Response data: Overall Response 64% (95% CI, 80,5%-46,0%): CR 34% PR 30%. Median response duration 6 months. Median actuarial survival 7 months. One year survival 30%. Median follow up 8 months.

CONCLUSIONS: 1.- Toxicity has been predominantly hematologic. 2.- Response and survival results are similar to those achieved with conventional chemotherapy. 3.- Nowadays we are conducting a new schedule with oral etoposide (50 mg/12h for 14 days) with better preliminar results.