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USE OF rHuG-CSF (LENOGRASTIM) TO DOSE INTENSIFY IN SMALL CELL LUNG CANCER (SCLC): A RANDOMISED STUDY. PJ Woll, J Hodgetts, L Lomax, N Thatcher. CRC Dept of Medical Oncology, Christie Hospital, Manchester, UK.

From July 1990 to October 1991, 67 consecutive SCLC patients with 0 or 1 adverse prognostic features (extensive disease, KP<60, Na<N, HCO_3<N, LDH>N, Alk Phos>1.5xN) were randomised to VICE chemotherapy alone (C) or with rHuG-CSF 5μg/kg/day sc (G). Chemotherapy comprised carboplatin 300mg/m^2 iv D1, ifosfamide 5g/m^2 iv D1, etoposide 120mg/m^2 iv D1+2, 240mg/m^2 po D3, vincristine 1mg iv D15. Cranial and thoracic irradiation were given after cycles 1 and 3. 6 cycles were given at intervals dependent on WBC≥3x10^9/l and platelets≥ 100x10^9/l. 65 patients were evaluable, 31 C and 34 G, median age 61 years (31-72). The groups were well matched for age, gender, all prognostic factors and blood count at entry. 50% of G patients completed 6 cycles of chemotherapy compared with 61% of C patients. Weekly WBC were consistently lower in C than G. Median WBC nadirs fell from 1.3 (C) and 1.8 (G) at cycle 1 (P=0.007) to 0.6 (C) and 1.1 (G) at cycle 6 (P=0.02). Median platelet nadirs were below 20 in both groups in cycles 4, 5 and 6. 76 episodes of febrile neutropenia occurred in 42 patients (65%). 6 patients died on study. Dose intensity (RDI) is expressed relative to a fixed 4 week cycle. Median RDI over 6 cycles was 1.09 (C) and 1.26 (G). For the first 3 cycles median RDI was 1.17 (C) and 1.31 (G). The response rates were 77% (C) and 85.3% (G). We conclude that rHuG-CSF permits dose intensity to be safely escalated in SCLC.

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LATE INTENSIFICATION (LI) AFTER INDUCTION CHEMOTHERAPY (ICT) FOR STAGE IIIB SMALL CELL LUNG CANCER (SCLC).

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Between 3/86 and 4/92, 42 stage IIIb pts with SCLC (median age 54 yrs) entered a program with ICT with epirubicin (90 mg/sqm/IV day 1) plus ifosfamide (3000 mg/sqm/IV days 1-2 plus Mesna) q 3 wks for 4 courses. In 18/42 patients VP16 (120 mg/sqm/IV days 1-2) was added to ICT. After restaging 25/38 pts in CR (9) or PR (16) were subjected to LI with high dose VP16 (1200 mg/sqm/IV in 4 days) plus cisplatin (120 mg/sqm/IV in 4 days) q 4 wks for two courses; 13/38 responders (CR 5, PR 8) not eligible for LI due to medical reasons were treated with conventional chemotherapy with cisplatin (80 mg/sqm day 1) plus VP16 (300 mg/sqm in 2 days) and local radiotherapy (RT) (8 cases) or surgery (2 cases), or local RT alone (3 cases). In the LI group RT was given to the chest and supraclavicular nodes (40-50 Gy), while prophylactic brain RT (30 Gy) was delivered only to pts in CR. After ICT, the CR+PR rate was 90% (CR: 33%; PR: 57%). After LI, 13/16 PRs were converted into CRs, while one pt in PR progressed. The 2-yr overall survival (OS) for all 42 patients who started this program was 50% and median OS was 24 mos (6-61+). In the LI group the 2-yr OS was 61%, median not yet reached; in the conventional consolidation group the 2-yr OS was 35%, median 16 mos. Myelosuppression was the main toxicity after LI. No treatment related death occured. In conclusion: 1) epirubicin plus ifosfamide +/- VP16 is an active induction regimen, 2) LI with cisplatin and high dose VP16 increases the CR rate, 3) LI may be associated with an improved 2-yr survival compared to other conventional consolidation treatments.

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EFFECTIVE REMOVAL OF SCLC TUMOR CELLS FROM BONE MARROW

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High dose chemotherapy with autologous bone marrow transplantation (ABMT) has shown promise in several types of cancer. There is, however, a risk of transfusing tumor cells with the BM cells, e.g. in patients with small cell lung carcinoma (SCLC). To eliminate SCLC cells from normal human BM, monoclonal anti- bodies reactive with SCLC cells were used with immunomagnetic beads and as immunotoxins (ITs) in model experiments. With 2 cycles of immuno-magnetic elimination the individual antibodies removed 2.5-4.4 log of H-146 tumour cells from a single cell suspension, as assessed in a highly reproducible soft agar assay. Different combinations of 2 antibodies were only margin-ally more effective than the individual MAbs, whereas 5-6 log removal was obtained with a combination of all 4 antibodies. Three immuno-toxins involving MAbs and Pseudomonas exotoxin A were highly active. Thus, more than 5 log removal was obtained with individual ITs at a concentration of 1.0 μg/ml, and with a mixture of all three ITs, each at a concentration of 0.1 μg/ml. The methods were equally effective when the tumor cells were mixed with BM cells at a ratio of 1:10. Neither of the procedures significantly affected the survival of normal progenitor cells, assessed in CFU-GM and CFU-GEMM assays. The results indicate that both methods can be used safely and effectively to eliminate tumor cells from the bone marrow in conjunction with ABMT in patients with SCLC.

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TAXOTERE IS ACTIVE IN SMALL CELL LUNG CANCER (SCLC) A PHASE II TRIAL OF THE EORTC EARLY CLINICAL TRIALS GROUP (ECTG)

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Taxotere, a semi-synthetic analogue of Taxol is prepared from needles of the Taxus baccatus, the european yew, and is twice as potent in preventing mitotic spindle microtubule depolymerisation. Myelosuppression is dose limiting but phase I toxicities include alopecia, skin reaction and hypersensitivity. This phase II trial tests 100mg/m^2 as 1 hr infusion q 3 wks in patients (P) with histologically proven locally advanced, unresectable or metastatic extensive SCLC, who received no more than 1 prior chemotherapy regimen. To date 27 P (5 female) median age 64 (44-73) have received 56 cycles of taxotere. Four were chemotherapy naive, 7 had received prior radiotherapy. Performance status was 0-1 in all but 2 P. Of 18 fully evaluable P 5 PR have been recorded. Toxicity showed neutropenia grade CTC III in 3 IV in 16 platelet nadir grade I-II in 3 P. Significant other toxicities were asthenia I-II in 9, III-IV in 5 P, alopecia and skin I-II in 16 P. Taxotere is clearly active in previously treated SCLC.

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ETOPOSIDE (VP-16) SCHEDULING IN SMALL CELL LUNG CANCER (SCLC), LABORATORY RATIONALE AND CLINICAL RESULTS.

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In vitro studies using the H69/P cell line and pilot clinical studies were performed to try to define an optimal schedule employing the DNA topoisomerase II poison VP-16 in SCLC. Following a 24 h exposure, the major VP-16-induced cell cycle block in H69/P occurred in G2 phase with a transient delay of cells in mid to late S phase at VP-16 concentrations ≥ 0.25 μM. Cells delayed in S phase showed up to 1.8-fold elevations in topoisomerase II levels compared with control cells in S phase, suggesting an oppurtunity for enhanced sensitivity to further treatment with topoisomerase poisons. Dye conversion assays (MTT) of culture growth showed that 24 or 48 h pretreatment with VP-16 resulted in greater than 2-fold enhancement of growth inhibition by mAMSA and VP-16.

A clinical study was designed based on these experimental results. 22 patients with untreated SCLC received VP-16 50 mg bd orally for 10 days, then VP-16 200 mg/m^2 i.v. on day 11, repeated every 21 days, to a maximum of 4 courses. Eleven (55%) of 20 assessable patients responded to therapy (10% CR, 45% PR). The median duration of PR was 6.3 months (range 4-23+ months), and of CR 8.5-22 months. 17 of the 22 patients have died, in whom median survival was 6 months. Modulation of topoisomerase II availability and enhanced sensitivity of VP-16-treated cells may assist the development of novel etoposide containing regimens with greater efficacy in SCLC.

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NEUROLOGICAL AND COGNITIVE IMPAIRMENT IN LONG TERM SURVIVORS OF SMALL CELL LUNG CANCER (SCLC)

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The role of prophylactic cranial irradiation (PCI) remains controversial in the management of SCLC because of concern about radiation induced neurological morbidity. 65 patients surviving ≥2 yrs in remission were assessed. 52 had had PCI. Patients were well: 95% performance status ≤1. Although 7% had WHO neurotoxicty grade ≥1, on neurological examination: 5% peripheral neuropathy, 11% cognitive deficit, 16% ataxia and 60% of 20 CT scans were abnormal. 81% showed impaired cognitive function (on tests of memory/information processing at speed) on ≥1 test, and 54% on 2 of the 4 tests used. The sample size was insufficient to see significant differences in PCI vs no PCI but test scores varied with initial chemotherapy and different radiation regimens. Results of multivariate analysis will be reported. A prospective randomised trial including neuropsychometric testing is in progress.