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CISPLATIN (P) / FLUOROURACIL (FU) AND ESCALATING DOSES OF VINORELBINE (VNB) FOR NON SMALL CELL LUNG CANCER (NSCLC).

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We have previously reported our experience in the treatment of NSCLC with P, FU by continuous infusion (CI) with folinic acid and VNB (ESMO 92); the major toxicities were neutropenia and mucositis. A dose-effect relationship has been suggested with VNB, and in order to improve the combination therapeutic index without increasing mucositis, we undertook a phase I-II study to determine optimum doses of VNB in combination with P and FU without folinic acid. From 9/92 to 2/93, 29 previously untreated patients (pts) with histologically proven measurable (CT scan) NSCLC were treated every 21 days (d) with FU (650 mg/m^2/d) by 24 hours CI d 1-4, P (100 mg/m^2) over 30 min on d 1, and VNB 18 mg/m^2 (7 pts, group A), or 20 mg/m^2 (15 pts, group B), or 22 mg/m^2 (7 pts, group C) IV d 1 and 8. Response evaluation was done after 2 or 3 cycles (cy). Results (WHO criteria, 2/93) are given separately for groups A, B and C. Pts characteristics: median age 59 (range: 41-71); 24 males (83%); performance status (KI) = 70% 7 pts, >70% 22 pts; histology: squamous and adenosquamous: 15 pts (52%), adeno: 7 pts (24%), large cell: 7 pts (24%); AJCC TNM stages: III a-b 15 pts (52%), IV 14 pts (48%). Toxicity: (WHO) neutropenia grade 3-4: group A (16 evaluable cy) 3/16 cy (19%); group B (42 evaluable cy) 16/42 cy (38%); group C (only 2 evaluable cy) 0/2 cy. Thrombocytopenia grade 3-4: group A 1/16 cy (6%); group B 2/42 cy (5%); group C 0/2 cy. Mucositis was uncommon and observed only in group B: grade 1-2: 3/42 cy (7%). There was no drug-related death. Activity: In group A (1 pt not evaluable because renal toxicity after the first cy) 3/6 pts achieved OR (50%, PR 3 pts); group B (1 pt too early), 8/15 pts achieved OR (53%), group C pts were too early. Conclusions: 1) this combination remains well tolerated with up to 22 mg/m^2 of VNB 2) the high overall response rate of 52% is encouraging. Enrolment is ongoing.

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PHASE II STUDY OF OXALIPLATIN (L-OHP) IN PATIENTS WITH ADVANCED NON SMALL CELL LUNG CANCER (NSCLC): Preliminary Results.

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Oxaliplatin, or trans-1-diaminocyclohexane-platinum (L-OHP) is a new platinum derivative whith antitumor activity observed in malignant melanoma, ovarian and colon carcinomas. Devoid of renal or hematologic toxicity, its dose limiting side effect is a cold-related, acute and reversible dysesthesia. Objective: to determine the efficacy and toxicity of oxaliplatin in advanced NSCLC patients (pts). Treatment: oxaliplatin was administered at 130 mg/m^2 as two hours infusion, repeated every 21 days. Eligibility criteria: included unresectable measurable histologically proven NSCLC, no previous treatment, ECOG PS 2 to 3 if stage I-III, PS 0 to 3 if stage IV, age of 75 years or less. Pts characteristics: from 1/92 to 1/93, 16 pts have been included. Median age 69.5 years (53-74); 13 males (81%); ECOG PS 0-1: 7 pts (44%) PS 2: 9 pts (56%); histology: squamous 9 pts, adeno 3 pts, large cell 3 pts, adenosquamous 1 pt, bronchioloalveolar 1 pt; AJCC TNM stages: I-III 7 pts, IV 9 pts. Major sites of metastasis included bone (6 pts), lung (3 pts), liver (3 pts), adrenal (2 pts). Activity: response was assessed after 2 courses except in case of evidence of progressive disease. 15 pts were considered evaluable for response (1 pt too early). 2/15 pts achieved PR (11 months, 6 months+) (13%), 3/15 achieved SD (20%), 2/15 achieved MR (13%). Toxicity: 48 cycles (cy) were evaluable. Toxicity was mainly neurologic. There was no leucopenia nor thrombopenia, WHO grade I anemia: 3cy. Nausea and vomiting grade I-II: 17cy (35%). Neither renal toxicity, nor hearing loss was observed. Reversible cold-related grade I dysesthesias of fingers, hands, toes and sometimes lips and nose occured in 39 cy (83%). Conclusions: 1) Oxaliplatin is potentially active as single-agent in pts with NSCLC. 2) this treatment is feasible in out patients in poor condition. 3) absence of hematological toxicity suggests that this drug is a candidate for multi-agent regimens in out patients. Enrolment continues.

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VINORELBINE IN THE TREATMENT OF NON-SMALL CELL LUNG CANCER

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In Phase II studies, Vinorelbine (VNR: a new semi-synthetic derivate of vinca alkaloids) has proved to be effective in non microcytic lung tumors with a remission rate of 33%. Between January 1992 and January 1993, we enrolled 43 pts, 36 male and 7 female, mean age 62 years (40-72), with lung neoplasia (histologic types: adenocarcinoma 16, epidermoid 11, large cell anaplastic 6, untyped 10; stage I, 1 pt; II, 1pt; IIIA, 7 pts; IIIB, 13 pts; IV 21 pts), 17 of whom had been pretreated. The total number of administered cycles was 205, with a mean of 13/pt in monotherapy and 4/pt in polytherapy. Today, 31 pts are evaluable (at least 3 cycles of therapy): 7 are still in treatment, 2 were lost to follow-up, 3 have died. The treatment schedules were:

1. VNR monochemotherapy 25-30 mg/sq.m/week = 4 pts;
2. VNR 25 mg/sq.m days 1-8 + CDDP 80 mg/sq.m on day 1 every 21 days = 31 pts;
3. VNR 25 mg/sq.m days 1-8 + CDDP 30 mg/sq.m days 1-2-3 + VP16 80 mg/sq.m days 1-2- 3 every 21 days= 6 pts;
4. VNR 25 mg/sq.m days 1-8 + CBDCA 300 mg/sq.m on day 1 every 21 days = 2 pts.

Results: CR 2/31 pts (6+/9 months); PR 10/31 (mean response duration 5.7 months); OR = 39%; NC 11/31 (mean response duration 5.3 months) = 36%; PRO 8/31 (26%).
Significant side effects: leukopenia WHO grade I, 34/205 cycles (16.6%); grade II, 11/205 (5.4%); grade III 8/205 (3.9%); grade IV 2/205 (1%); and anemia WHO grade I 14/205 cycles (6.8%); grade II 6/205 (2.9%); grade III 3/205 (1.5%); grade IV 2/205 (1%).
Similar to others reported in the literature, the results are promising, also considering that for the toxicity encountered in the evaluable pts, the dose intensity of the administered drugs was only 0.57±0.17.

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PALLIATIVE BRONCHOSCOPIC ELECTROSURGERY IN LUNG CANCER

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Bronchoscopic electrosurgery (BE) was performed in 12 patients (pts), mean age 64 years (range 48-82). One patient had hemoptysis, 11 had obstructing tumors. All treatments were performed under topical lidocaine anesthesia and midazolam sedation. Treatment was monitored by a pulse oximeter. Complications were a hydropneumothorax 10 days post-BE and one case of pneumonia. Bleeding was always minimal and easily manageable. In 8 pts. intraluminal tumor debulking was significant. In three pts. extraluminal tumor compression was found. Hemoptysis resolved in one patient. Dyspnea improved in 5/11 pts, all with mainly intraluminal tumors. Longest follow up was 8 months. Recurrences were assessed between 2-6 months in 3 pts, two of which subsequently received brachytherapy and one pt. received radiotherapy. The remaining pts. did not show endobronchial tumor progression. BE is cost effective for endobronchial tumor debulking and can be easily used to manage hemoptysis. But effects on reopening the airways are clearly related to extraluminal tumor (re)growth.

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NEOADJUVANT THERAPY FOR UNRESECTABLE STAGE III NON SMALL CELL LUNG CANCER (NSCLC).

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From 3/90 through 12/92, 25 patients with unresectable stage III NSCLC were treated with radiotherapy (50 Gy) and 2 cycles of continuous cisplatin (25 mg/ sq. m/24 hrs) on days 1-4 and VP-16 (100 mg/sq. m/day) on days 1 and 3. Three to six weeks after treatment, 14 patients proceeded to thoracotomy and successful resection (6 by pneumonectomy and 8 by lobectomy). The resectability rate was 56%.

Complete sterilization of tumor was achieved in 2 patients (8%) and shrinkage of tumor was noted in 10 patients (40%). The median survival to date for all 25 patients is 13 months, and for the 14 resected patients, the actuarial two-year survival is 50%. The preliminary results indicate that the above neoadjuvant regimen is tolerable and could offer significant (p = 0.014) improvement in the survival of patients with unresectable stage III NSCLC.

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VINORELBINE (VB)+ CISPLATIN (DDP)+ ETOPOSIDE (E) IN THE TREATMENT OF NON-OPERABLE NON SMALL CELL LUNG CANCER (NSCLC).

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Between 1/92 and 10/92, eighty Pts (67 M, 13 F), mean age 59 Y, median ECOG P.S.1 (0-2), 26 stage IIIb and 54 stage IV, have been enrolled in a Phase II clinical trial in which VB, DDP and E were given respectively at 25 mg/sqm on days 1,8; 30 mg/sqm on days 1-3 and 80 mg/sqm on days 1-3; cycle repeated on day 21. All Pts are evaluable for toxicity and 66 for activity being 14 Pts excluded for early death(9 Pts), severe toxicity(2 Pts), refusal(2 Pts),PD (1 Pt) before the first evaluation. The histologies: 22 Adeno, 38 squamous well differentiated, 16 squam. poorly differentiated, 2 bronchioloalveolar, 2 not specified. Three hundred and twenty four cycles have been administered, median 4 cycles/Pts (1-9), 101 cycles (31.2%) have been reduced and 13 (4%) delayed for toxicity. Out of 80 Pts, 3 (3.8%) and 32 (40%) respectively achieved CR and PR, while 23 (28.7%) were SD and 8 (10%) progressed, 14 are not evaluable. Grade 3 and 4 hematologic toxicity have been registered in 55 cycles (17%) for WBC, in 19 (5.8) for Hb, and in 5 (1.5%) for PLT. On the whole, the protocol may be considered very active for NSCLC:43.8% OR [53% of 66 evaluable Pts] is a figure that may be compared to the best treatments; however, in our hands this combination of three drugs was not well tolerated: 80 Pts were scored ECOG 0-2 at the beginning of the treatment, but at the end 13 Pts were in P.S. 3 or 4; 9 early deaths occured in Pts probably under-scored. In conclusion we consider the combination of VB + DDP +E as a very active treatment for NSCLC Pts with high P.S.; a pilot study with 20% reduction of the VB and DDP doses is ongoing. We believe that in the near future the addition of growth factors or the reduction of the doses will optimize this interesting three-drug regimen.