1092 PUBLICATION

INTRACELLULAR DIACYLGLYCEROL: A MITOGENIC SECOND MESSENGER PROPOSABLE AS MARKER OF TRANSFORMATION IN SQUAMOUS CELL CARCINOMA OF THE LUNG

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We examined 50 patients with unilateral lung cancer. Bronchial lavage provided neoplastic and normal cells in which we studied a mitogenic second messenger, diacylglycerol, that is associated with early stages of transformation. Level of diacylglycerol in cells from the affected side was compared with that from the control side, thus providing a control for each patient. Diacylglycerol in lavage fluid from the affected bronchus was elevated in 60% of the patients. This elevation reached 73% in patients with squamous cell carcinoma, a sensitivity higher than "traditional" markers for lung cancer. These findings may have significant implications for the use of diacylglycerol as a novel marker for early detection of lung cancer, and for monitoring recurrences.

1093 PUBLICATION

CDDP+NVB ASSOCIATION CHEMOTHERAPY IN STAGE III–IV NSCLC. RESULTS OF A PHASE-2 STUDY

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North Milan Group presents a phase II study, including CDDP+NVB combination therapy, conducted between April 1992 and September 1994 on 115 patients (pts) with NSCLC. Pts characteristics are: Stage IIIa: 21, IIIb: 54, IV: 40; Median age: 63 (range: 40–74); PS: ECOG 0– 1 (Karnofsky 100–80): Male/Female: 103/12; Squamous Cell Carcinoma; 61, Adenocarcinoma: 42, Large Cell Carcinoma: 12; No Weight loss $\geqslant$ 10%. All pts were previously untreated and showed measurable disease. Cisplatin (CDDP) 80 mg/mg on day 1 + Vinorelbine (NVB) 25 mg/mg on day 1 and 8 were administered intravenously every 21 days, for 3 standard courses in all. Toxicities were evaluated after every course, responses after 3 cycles. Pts evaluable for response were 111/115 (2 pts died before the last cycle of chemotherapy, 2 pts were lost at follow-up). Objective responses (CR+PR) were documented in 58 pts (overall response rate 52.2%): 29 NC (26.3%), 24 P (21.8%). Among stage-III pts, 33 PR and 12 NC received radiotherapy on the chest; 8 pts in all received palliative radiotherapy on methastatic bone lesions. Ten pts (6 IIIA and 4 IIIB) were reconducted to surgical treatment: 7 pneumonectomies, 2 lobectomies and 1 segmentectomy were performed. Medical time to progression (TTP) was 7 months (ms). Medical survival time (MST) ranged from 4 to 30 ms: in particular it was 14 ms for PR, 7 ms for NC, 6 ms for P pts. Median survival rate is 10 ms. 34 pts are now alive: 26 pts at 12 ms or more, 4 pts at 24 ms or more. Cycles administrated in all were 353; 17 cycles (5%) were postponed because of intercurrent neutropenia <1000/mmc. After G-CSF treatment, the scheduled cycle was effected by 7 days at most. Significant side effects (WHO III–IV) were: nausea-vomiting in 45 cycles (12.7%), leukopenia in 40 cycles (11.3%), phlebitis in 29 cycles (8.2%). anaemia in 21 cycles (6%) constipation in 17 cycles (5%). Other haematological toxicity, neurotoxicity, nephrotoxicity, cardiotoxicity and alopecia not commonly occurred, anyhow under WHO III grade. PS remained on precedent value (except for P pts). No weight loss > 10% was ever recorded. Quality of life was reported as obtimal during all the treatment. We conclude this CDDP+NVB trial shows evident validity in terms of activity, efficacy, tolerability and applicability in out patients. Survival increment and III-stages surgical reconduction are still modest, yet our results are totally comparable to others including Vinorelbine in two-three drugs association chemotherapy on NSCLC.

1094 PUBLICATION

A DOSE ESCALATION STUDY OF CARBOPLATIN PLUS VINORELBINE FOR ADVANCED NON-SMALL CELL LUNG CANCER

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Platinum compounds and vinorelbine have been demonstrated to be active in non-small cell lung cancer (NSCLC). A dose-response relationship with platinum-based chemotherapy has been suggested for a number of malignancies including NSCLC. The aims of the study were to assess tolerability and optimal dose-intensity of increasing doses of carboplatin (300 mg/m^2 level 1, 350 mg/m^2 level 2, 400 mg/m^2 level 3, day 1) in association with a fixed dose of vinorelbine (25 mg/m^2 days 1 and 8) without G-CSF in advanced NSCLC. Thirty-eight patients entered the study and are evaluable for toxicity and response. Patients were untreated with systemic chemotherapy, had TNM stage IIIB–IV, performance status ECOG 0–2, and their median age was 62 years (range, 41–70). The number of patients evaluable on each dose level was 14 (level 1), 14 (level 2) and 10 (level 3, current level). A total of 142 courses was delivered (median per patient, 4 courses). Non-hematologic side effects included grade I–II mucositis (8%), neurotoxicity (6%), and nausea (4%). No significant difference was observed for the 3 groups. The incidence of myelotoxicity was highest in the group of patients at level 3, with grade III–IV neutropenia observed in 20% of the cases and grade I–II thrombocytopenia in 30% of the patients, which was reversible and of short duration. No drug-related death has been observed, and only 1 patient at level 3 had a grade I infection. Objective remission was observed in 2/14 patients at level 1, in 3/14 patients at level 2, and in 3/10 patients at level 3. In conclusion, the combination of carboplatin at the dose of 400 mg/m^2 day 1 and vinorelbine at the dose of 25 mg/m^2 days 1 and 8 can be safely administered without G-CSF as first-line cytotoxic therapy for advanced NSCLC and warrants further evaluation.

1095 PUBLICATION

A PHASE II STUDY OF CPT 11 (IRINOTECAN 350 MG/M^2 EVERY 3 WEEKS) IN UNTREATED NON-SMALL CELL LUNG CARCINOMAS

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Patients with untreated, stage IV, non small cell lung cancers (NSCLC); aged $\leqslant$75; WHO PS $\leqslant$1; normal hematologic renal and hepatic baseline value have been selected for (treatment with the new Topolsomerase I inhibitor CPT 11 delivered as a 30′ IV infusion every 3 weeks at the dose of 350 mg/m^2. Nineteen patients have been so far entered (M/F: 15/4; median age 62 (41–75); PS 0: 26%, 1: 63%, 2: 11%); median number of involved organs: 3 (1–6) with lung in 30%, mediastinum in 21%, bone in 8% and liver in 5% of patients.

All patients but one were chemotherapy naive.

Patients have received 74 cycles (96% at the planned dose) and the median Relative Dose Intensity was 0.99.

Efficacy: (Preliminary Results) PR: 4; NC: 5; PD: 6; not evaluable: 4.

Safety: The following grade 3 or 4 toxicities have been observed: (% of patients) neutropenia: 28%; delayed diarrhea: 26%; nausea/vomiting: 26%; anemia: 22%. An early cholinergic-like syndrome, never severe, was frequently observed. The most common symptom was diffuse sweating in 16% of patients. One toxic death occurred due to the combination of diarrhea and infection.

Conclusion: Severe neutropenia combined to severe diarrhea is the limiting toxicity. From these preliminary results, CPT 11 could be an effective drug in NSCLC, as formerly shown in Japanese studies.

1096 PUBLICATION

PRELIMINARY REPORT OF A PHASE II STUDY OF DOCETAXEL (TAXOTERE® AND CISPLATIN IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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Docetaxel is a tubulin polymerizing agent that shows activity as a single agent in advanced NSCLC. Its combination with cisplatin has been investigated in different phase II trials. In this study, we used a treatment schedule consisting of docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2 every 3 weeks during 3 cycles and then every 6 weeks, with a standard premedication: dexamethasone, antihistaminic, antiemetic and hyperhydration. Evaluation of activity was performed every 6 weeks. Eligible patients (pts) had histologically proven locally advanced or metastatic

NSCLC, measurable tumor, no previous chemotherapy, KPS ≥60, age ≤75, normal hematological, hepatic and renal functions, no brain or leptomeningeal involvement and signed informed consent. Fifty-one patients have been included: 3 were not eligible, the characteristics of the 48 remaining pts are: 44 males, 4 females; mean age: 54 years (range 34–75); stage IIIB: 13%, stage IV: 87%; they received a mean of 4 cycles (range 1–6). Among these 48 pts, 1 CR and 13 PR (29%) were observed, including 9 PR confirmed today by an independent panel, lasting from 15+ to 31+ weeks. Main toxicities (G 3–4) were: febrile neutropenia: 5 pts, documented sepsis: 5 patients. No toxic death was reported. As a result of using routine premedication, previously reported side effects were considerably lessened. Based on this preliminary analysis combination of docetaxel 75 mg/m^2 and cisplatin 100 mg/m^2, indicates an interesting result which should deserve other investigations of this drug combination.

1097 PUBLICATION

THE INFLUENCE OF SEX, AGE AND HISTOLOGY ON TREATMENT RESULTS OF RADICALLY TREATED PATIENTS WITH LOCALLY ADVANCED, NON-SMALL CELL LUNG CANCER RADIATED WITH CURATIVE INTENT

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In prospective, randomized study the influence of sex, age and histology on the prognosis and survival of 190 patients with inoperable, non-small cell lung cancer was examined. The patients have been treated with curative radiotherapy with tumour dose of 60 Gy, accomplished in two different radiation techniques: split course and continuous course with reduced additional field. There was not a statistically significant influence in obtained response and survival according to prognostic factors mentioned above. Three years survival rate was statistically higher in radically treated women (26.3%) compared with radically treated men (11.6%). In the age group of 50 to 59 years three years survival rate was 17% and it was higher compared with survival rate achieved in the other age groups. The obtained objective response had a significant influence on survival rate independently of histology.

1098 PUBLICATION

EXPRESSION OF SEVERAL BIOLOGIC MARKERS AS PROGNOSTIC FACTORS IN PATIENTS WITH NON-SMALL CELL LUNG CANCERS

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Despite modern diagnostic, staging, and therapeutic advances, esp. with molecular biologic techniques, the 5-year survival rate of all cases of lung cancer does not exceed 15%. With better understanding of tumor biology, one may improve survival through proper treatment. Here we present the clinical significance of several biologic markers as prognostic markers in patients with non-small cell lung cancers. The survival has correlated with the expressibility of proliferative cell nuclear antigen (PCNA), epidermal growth factor receptor (EGFR), p53 and/or blood group antigen A (BGAA) using immunohistochemistry in 46 cases patients with non-small cell lung cancers. The results were as follows: (1) The expression of BGAA was correlate with better survival in median survival and in 2-year survival and that of PCNA was correlated with worse survival in median survival and 2-year survival rate. (2) The expression of EGFR or p53 was not valuable to predict prognosis in non-small cell lung cancers. (3) With simultaneous applications of PCNA, EGFR and p53 immunostain, the patients with 2 or more negative expressions showed better prognosis than the patients with 2 or more positive expressions. In conclusion, it is suggested that the expression of blood group antigen may be a positive prognostic factor and that of PCNA may be a negative prognostic factor and also, the combination of expressions of PCNA, EGFR and p53 may be used as a negative prognostic factor.

1099 PUBLICATION

CISPLATIN (CDDP), 5-FLUOROURACIL (5FU) AND VINORELBINE (NVB): A PHASE II STUDY IN ADVANCED NON SMALL CELL LUNG CANCER (NSCLC)

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Thirty-three patients, 25 males, 8 females, median age 55 years (37–70), with histologically proven measurable (CT scan) NSCLC were treated at Institut Curie with a three drug combination chemotherapy. The regimen consisted of CDDP 25 mg/m^2 continuous infusion (CI) days 1 to 5, 5FU CI 600 mg/m^2 days 1 to 5 and NVB 25 mg/m^2 on days 1 and 5. Cycles were repeated every 28 days.

Staging of these unresectable or inoperable tumors was as follows: stage IIIA (5 pts), stage IIIB (15 pts), stage IV (13 pts). PS 0–1 (26), PS 2 (7). 94 courses of chemotherapy were delivered. Response evaluation was done after 2–3 cycles. One patient died of complications from an ischemic cerebrovascular stroke after the third cycle. 32 pts were evaluable. Partial response was achieved in 11/20 stage III pts (55%) and in 7/12 stage IV pts (58%). Nine patients had a minor response or stable disease and 2 patients progressed. WHO grade 4 toxicities were leucopenia 31%, thrombocytopenia 4%, mucositis 4%. The tolerance is acceptable and the overall response rate is encouraging.

1100 PUBLICATION

CONCURRENT DAILY CHEMOTHERAPY WITH HYPERFRACTIONATED THORACIC IRRADIATION IN STAGE IIIA & B NSCLC

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In January 1993 we initiated a pilot study of concurrent daily chemotherapy with hyperfractionated thoracic irradiation in Stage III NSCLC. Twenty-four patients were entered on study. The following were the demographics: 15 males and 9 females; median age 62 (35–77); mean performance status 0; histology—10 squamous, 3 adeno, 11 large cell carcinomas; stage—11 with IIIA, 12 with IIIB, 1 with IV. Chemotherapy consisted of CDDP 3 mg/m^2 daily (4 pts), 5 mg/m^2 daily (1 pt) and 6 mg/m^2 daily (19 pts), with weekly vinblastine 2 mg/m^2 (9 pts). Hyperfractionated thoracic irradiation 60 Gy in 40 fractions over 4 weeks at 1.5 Gy b.i.d. Four weeks post concurrent chemo-irradiation, 3 cycles of CDDP 75–80 mg/m^2 and vinblastine 8 mg/m^2 q 21 days were given. Overall response rate 18/24 (75%), CR 7/24 (29%), PR 11/24 (46%). Median time to progression 12.4 months, median survival 17.3 months. The major toxicity was esophagitis. The toxicity will be presented in detail.

1101 PUBLICATION

THE NEW POSSIBILITIES OF THE AUTO-LYMPH CHEMOTHERAPY NON-SMALL CELL LUNG CANCER

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The original Auto-lymph chemotherapy (ALCT) method includes extra-corporal incubation of the lymph, derived from the ductus thoracicus, with 120–130% of VAM, CAM, CAF, FEP doses. The reinfusion of the mixture leads to considerable treatment effects. The ALCT method was used in 47 lung cancer patients (27 with stage IIIB and 20—stage IV of disease), with 76.6% of marked partial tumor regressions and not a single case of progression.

As it was found, the regimen: 5-Ftoruracil 750 mg/m^2—1, 2, 3 days; Vepesid 100–150 mg/m^2—1, 2, 3 days; CDDP 100–120 mg/m^2—4th day—turned to be the most effective. This regimen was used in the treatment of 10 patients (6 with stage IIIB and 4—stage IV of disease), with 50.0% of marked partial tumor regressions. The investigation of ALCT-effect revealed the improvement of the immune status' parameters, the signs of immune stimulation. (An increase in the level of IL-I; IL-2; IL-6; TNF. FGA-response stimulation.) Cytotoxic activity of lymphocytes from the lymph (LL) in relation to transferred pulmonary carcinoma cells with the use of MTT-assay. The LL cytotoxicity revealed 1.5–3.0 fold increase after incubation with 5-ftoruracil (1500 mg/l) and vepesid (200 mg/l), with the maximal activity at the 3rd–5th day. Then, the activity decreased and turned to the initial level by the end of the third week.