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