1044 POSTER

Vesnarinone inhibits growth of small cell lung cancer cell lines via induction of apoptosis

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Purpose: Vesnarinone is a positive inotropic agent that is used for treating congestive heart failure. Recently, it has been shown to inhibit *in vitro* the growth of several tumor cell lines, suggesting a potential for treating cancers. We have now examined the effect of vesnarinone on small cell lung cancer (SCLC) cell lines and induction of apoptosis.

Methods: Five SCLC cell lines, LC02, LU134, LU65A, LU65B, LU65C, were obtained from JCRRB. Growth inhibition of the cells by vesnarinone was assayed with ^{3}H-thymidine incorporation after 72 hr culture. Induction of apoptosis in the cells pretreated with vesnarinone was examined by the *in situ endlabelling* (ISEL) method and gel electrophoresis. Expression of Bcl-2 and Fas antigens was detected by FACS analysis.

Results: Vesnarinone inhibited ^{3}H-thymidine incorporation in a dose-dependent manner at concentrations from 0.1 to 20 μg/ml in the cell lines. Maximum suppression was obtained at a concentration of 20 μg/ml: 40%, 60%, 46%, 37%, and 38%, respectively. ISEL method showed that vesnarinone induced apoptosis in LU65A cells. Gel electrophoresis showed DNA fragmentation in LU65A cells. Vesnarinone induced the expression of Fas antigen, but did not affect the expression of Bcl-2.

Conclusion: Vesnarinone showed growth inhibition of SCLC cell lines. Fas expression may be one pathway of apoptosis induction by vesnarinone. These results suggest that vesnarinone may be useful in treating SCLC.

1045 POSTER

Phase II trial of the multi-targeted antifolate LY231514 (MTA) as first-line therapy for patients with advanced non-small cell lung cancer (NSCLC)

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Purpose: We are conducting a prospective, single cohort study to determine the efficacy and safety of LY231514 in patients with advanced NSCLC.

Methods: Twenty-seven chemotherapy-naive patients (pts) with advanced NSCLC were treated with LY231514 as a 10 minute iv infusion every 3 weeks. The starting dose for the first 3 pts was 600 mg/m^2; due to toxicity on this and another MTA trial, it was reduced thereafter to 500 mg/m^2. Patients were evaluated for tumour response and toxicity.

Results: As of January 23, 1997, baseline information is available on 25 patients; to date, 21 are evaluable for toxicity and 17 are evaluable for response. The median age is 63, 18 pts are male, 24 have ECOG PS 0/1, 13 have adenocarcinoma and 7 have squamous cell histology. Five pts have had a partial response (29.4%; 95%CI 10.3–55.9). In a total of 70 cycles of treatment, 8 pts had gr 3/4 neutropenia, 1 pt had gr 4 thrombocytopenia, and 3 pts had febrile neutropenia. Gr 3/4 non-hematologic toxicities included skin rash (8/21), lethargy, nausea +/− vomiting (5/21 each), arthralgia, diarrhea, and anorexia (2/21 each).

Conclusions: LY231514 shows moderate activity as a single agent in this setting and can be given safely. The trial will close when 30 evaluable pts have been accrued and final results will be presented at this meeting.

1046 POSTER

A summary on dose escalation using CHARTWEL in non-small cell carcinoma of the bronchus

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Following the success of the CHART randomised controlled trial in non-small cell carcinoma of the lung where accelerated radiotherapy gave a 9% increase in 2 year survival, further pilot studies have been carried out in dose escalation to increase the chance of local tumour control. CHARTWEL (CHART-WeekEnd-Less) has been piloted on the grounds that overall time is the most important radiobiological factor and weekend treatment is difficult for many centres in the United Kingdom and Europe.

56 patients have been entered into this Phase I study. The first 16 received 54Gy in 36 fractions over 16 days; the dose was then escalated by keeping the dose per fraction the same and increasing the number of fractions. Seven patients received 57 Gy, 10 58.5 Gy and 23 60 Gy in 40 fractions over 18 days. Despite the dose escalation there was no increase in acute morbidity as monitored by the severity and length of time of oesophagitis. The complete regression rate is 20% in this advanced group of patients and the survival is almost identical to those entered into the CHART randomised controlled trial. Dose escalation beyond 60 Gy has been attempted but planning becomes difficult because of surrounding normal structures.

It is now planned to pilot CHARTWEL with neo-adjuvant and then concomitant chemotherapy.

1047 POSTER

Carboplatin plus vinorelbine: A new active regimen in extensive small cell lung cancer. Results of a multicenter phase II study

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Purpose: Vinorelbine is a new vinca alkaloid that showed activity in small cell lung cancer (SCLC) with about 30% of objective response (OR) in untreated patients (pts). To date there is no report in the literature on vinorelbine containing combination chemotherapy, even with platinum compounds, in SCLC. In attempt to evaluate a new chemotherapy regimen, we conducted a phase II study on carboplatin plus vinorelbine in pts with extensive SCLC aged 70 years.

Methods: All pts received carboplatin (300 mg/m^2, i.v., d 1) and vinorelbine (25 mg/m^2, i.v., d 1 and 8), recycled every 4 weeks. Thirtyseven chemotherapy naive consecutive pts entered the study. The pts, 33 males and 4 females, had a median age of 64.5 years (range 46–70), PS (ECOG) was 0 in 6 cases, 1 in 12 and 2 in 19.

Results: We observed 73% OR (CR + PR), with 27% complete response. Median time to progression was 7 months. Median survival has not been reached. The treatment was well tolerated with mainly mielotoxicity.

Conclusion: These data show that carboplatin plus vinorelbine is a new active and well tolerated regimen in extensive SCLC. In view of activity, low toxicity and easy administration it may be a reasonable option in out-patients treatment.

1048 POSTER

Expression of bcl-2 protein in non-small cell lung carcinoma (NSCLC)

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Purpose: The protooncogene bcl-2 encodes a protein which regulates cell death (apoptosis). The protein is expressed in basal cells of normal bronchial epithelium. No sufficient data are available, however, for its expression in bronchogenic carcinoma. The aim of this study is to examine the expression of bcl-2 protein in NSCLC and its clinical implications.

Material and Method: Imprint smears of lung specimens from 60 consecutive patients (46 male/14 female, 42–81 [mean: 60.5] years old) who underwent resection for primary NSCLC, were studied immunocytochemically by APAAP method. Postoperative staging of these patients showed 12 of them (20%) to have stage I disease, 14 (23%) stage II, 20 (33%) stage IIIa, 10 (17%) stage IIIb and 4 (7%) stage IV disease. Sixteen patients were found to have low grade and 44 high grade tumours. The patients were followed up for 2–36 (20.1 ± 12.0) months. A correlation of bcl-2 protein expression in tumour cells to the histological type and grade of the tumour, the clinical stage of the disease as well as the patients' survival was attempted.

Results: Expression of bcl-2 protein was detected in 12/38 (31.5%) of squamous cell carcinomas and in 4/22 (18.1%) of adenocarcinomas ($p > 0.1$). No relationship of bcl-2 protein expression to the grade of the tumour or the stage of the disease could be established. Relationship between bcl-2 expression and survival of the patients was found.

Conclusions: bcl-2 protein is expressed in some NSCLC and may be used as a prognostic parameter of the disease.