168 POSTER

Chemotherapy followed by three-times daily hyperfractionated accelerated radiotherapy in stage IIIa (PN2)/IIIb non small cell lung cancer

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Introduction: No useful information is available on induction chemotherapy (CT) followed by three-times daily hyperfractionated accelerated radiotherapy (three fractions per day; hfRT) in locally advanced non-small cell lung cancer (NSCLC).

Patients and methods: Since February 1998, 49 patients (pts) with locally advanced NSCLC proved by mediastinoscopy entered a prospective study with induction CT followed by surgery, if suitable, and hfRT. Chemotherapy consisted in 3 cycles of cisplatin 80 mg/m2 d1 plus gemcitabine 1250 mg/m2 dd1,8 q3w (after cisplatin 100 mg/m2 d1 plus gemcitabine 1000 mg/m2 dd1,8,15 q4w was given to the first 10 pts all of whom required dose reduction/treatment discontinuation). Radiotherapy consisted of 54.4 Gy (1.2 + 1 + 1.2 die, 5 days/week) for patients treated with surgery and in 64.6 Gy (analogue fractionation) in all the others. Surgery was planned after CT in stage IIIa-pN2 patients with resectable disease.

Results: Chemotherapy obtained 75% response rate (95% CI: 57-87%) in 40 pts evaluable for response (9 pts: too early).

At present 28/36 pts staged IIIa-pN2 completed CT, 27 underwent surgery (R0: 24 pts) and 32 completed hfRT. With a median follow-up of 8.7 mths, 24 pts are alive with a 1 and 2ys survival estimated as 63% (95%C.I:47-85%) and 47% (95%C.I:29-79%), respectively.

All the 13 pts with stage IIIb NSCLC received hfRT: 12 completed the treatment and 9 pts died for disease progression with a median survival of 13 mths.

One postoperative death and 2 major surgical complication occurred. Three cases of RTOG grade 3 esophagitis were registered, with hfRT interruption in 1 case.

Conclusion: Induction chemotherapy followed by three-times daily hyperfractionated accelerated radiotherapy in locally advanced NSCLC is feasible and effective. Completion of the study and longer follow-up will be presented.

169 POSTER

A phase I/II study of twice-weekly gemcitabine and concurrent thoracic radiation for patients with locally advanced non small cell lung cancer (NSCLC)

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Introduction: 2'2'-difluoro-2'-deoxycytidine (Gemcitabine) is a fluorine-substituted cytarabine (Ara-C) analog that is an active agent in NSCLC and has significant radiation sensitizing properties. In an attempt to take advantage of its radiation sensitizing activity, we proposed a strategy to maximize the local radiation effect through the use of a concurrent twice-weekly gemcitabine schedule. Pre-clinical data from our laboratory and others, have shown that sensitization with gemcitabine is enhanced as the dosing frequency is increased. Therefore, we have attempted to determine the maximum tolerated dose (MTD) and efficacy of induction gemcitabine/carboplatin followed by twice-weekly gemcitabine and concurrent thoracic radiation in patients with stage IIIa/IIIb non small cell lung cancer (NSCLC).

Patients and Methods: 28 patients with histologically confirmed stage IIIa and IIIb NSCLC were studied. Patients received induction gemcitabine (1000 mg/m2) and carboplatin (AUC 5.0-5.5) for two - 21 day cycles. This was followed by escalating doses of gemcitabine administered via a 30 minute intravenous infusion twice-weekly for six weeks concurrent with 60-74 Gy of thoracic radiation. All thoracic radiation was delivered using 3-dimensional treatment techniques.

Results: Of the 28 patients entered, 17 were entered during the phase I portion of the study. The dose-limiting toxicity of twice-weekly gemcitabine was observed at 50 mg/m2 given twice-weekly (100 mg/m2/wk) and was grade III pneumonitis observed in one patient, grade III pulmonary fibrosis in a second patient and grade IV esophagitis observed in 2 additional patients. Twice-weekly gemcitabine at a dose of 35 mg/m2 was determined to be the MTD. The overall response rate for the 16 evaluable patients treated on the phase I was 88%. Toxicities observed for the 11 patients receiving induction and concurrent therapy was primarily neutropenia and thrombocytopenia. The median survival for the patients treated on the phase I portion of the study is an encouraging 16.0 months.

Conclusions: The maximum tolerated dose of twice-weekly gemcitabine is 35 mg/m2 (70 mg/m2/wk) given concurrent with thoracic radiation. These preliminary data would suggest this is an active regimen for the treatment of locally advanced NSCLC. A multi-institution Cancer and Leukemia Group B (CALGB) phase II study to ascertain the potential efficacy of this regimen is in development.

170 POSTER

Taxol-gemcitabine-vinorelbine (TGV) given every 2 weeks in chemo-naive advanced NSCLC. A SICOG phase I study

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Background: In a previous dose-finding study we selected the MTD of paclitaxel (T) (70 mg/sqm) when given with fixed doses of gemcitabine (G) (1,000 mg/sqm) and vinorelbine (V) (25 mg/sqm) on d 1&8 q3wk in advanced NSCLC patients. (Lorusso et al. ASCO 2000; 19:527a).

Purpose: To determine whether a higher dose intensity of gemcitabine and paclitaxel could be delivered by using an every-2 week schedule.

Patients and Methods: Chemonaive patients (pts) with locally advanced or metastatic NSCLC, age 18-70, and ECOG PS 0-2 were eligible. V was given every 2 weeks at a fixed dose of 25 mg/sqm, together with G and T at starting doses of 1,000 mg/sqm and 80 mg/sqm, respectively. G and T doses were escalated alternately by 250 mg/sqm and 20 mg/sqm respectively, until DLT occurred at cycle I in more than 33% of patients of a given cohort.

Results: As of April 5, 47 pts (median age 62; M/F = 38/9; stage IIIB/IV= 15/32; PS 0-1/2= 28/19) have been accrued, through 8 different dose levels, for a total of 153 cycles delivered. Doses of G and T of 1,500 mg/sqm and 150 mg/sqm have shown to be well tolerated (only 1 case of lack of hematologic recovery on d 15 at cycle I). Since we have considered the dose intensity of these 2 drugs satisfactory, we have decided to increase the dose of vinorelbine by 5 mg/m2 at each step. Two step have been completed in this way (vinorelbine 30 mg/m2 and 35 mg/m2), without encountering severe hematologic and nonhematologic toxicity. If all the 153 delivered cycles are considered, grade 3-4 neutropenia and thrombocytopenia have occurred in 18(39%) and 5 (11%) pts. Red blood cell transfusions have been required in only 4 patients. Fatigue, constipation, and peripheral neuropathy have been the most common nonhematologic side effects, although only 4 patients have shown severe nonhematologic toxicity. Nausea and vomiting have been generally mild. Thirty pts. are presently evaluable for response. One complete and 10 partial responses have been recorded for a 37% ORR.

Conclusion: The adoption of an every-2 week schedule allows the delivery of a higher dose-intensity of paclitaxel, and gemcitabine without impairing the tolerance of the treatment. The accrual still continues to define the MTD of vinorelbine, and we expect that the final results of the dose escalation will be available at the time of the meeting.

171 POSTER

Use of 3-dimensional conformal radiation therapy (3DCRT) for radiobiologically escalated dose for non-small-cell lung cancer (NSCLC)

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Rationale: Local control in patients (pts) with unresectable NSCLC has to be improved. 3DCRT allows dose escalation by sparing normal tissues, but to date most of the trials have increased dose by prolonging treatment duration. The enhancement of therapeutic ratio may be wasted by excessive treatment duration allowing tumour repopulation. We postulated that the therapeutic ratio of 3DCRT could permit dose and time escalation by increasing the fraction size (fr).

Aim: To assess the feasibility of a hypofractionated accelerated high-dose radiotherapy regimen (72 Gy/24 fr, 3 Gy/fr). Its biological effects are compared to a standard treatment in Table 1.

Methods: There were 15 pts with a histologically or cytologically proven NSCLC with KPS>70% and weight loss <10% in 3 months, with stage I/II medically inoperable (n=5) or stage IIIa/b without pleural effusion (n=10). Induction chemotherapy was used in 6 pts. The mean treatment time was 34 days (30 to 41). No more than 30% of the combined lung volume received more than 25 Gy and the maximum dose to the spinal cord was < 61%.