Results: We enrolled into the study 35 patients with median age 54 years (range 24-75). 18 patients were male, 17 female. 27 patients had malignant pleural mesothelioma, 8 malignant peritoneal mesothelioma. 3 patients were sarcomatous subtype and 2 mix subtype. Remaining patients were pure epithelial subtype. Median 4 cycles (range 1-7) of chemotherapy were administered. Response to chemotherapy was determined in 22 patients who received 2 or more cycles of chemotherapy. There was no complete remission. The partial response rate (PR) was 36.3%. Stable disease was obtained in 36.3% of patients. Estimated overall survival (OS) and progression free survival (PFS) were 12±3.88 (95% CI 4.39-19.61) and 9±3.12 (95% CI 2.88-15.11) months respectively. 2 years survival rate was calculated as 22.0% and 2 years PFS rate 15.7%.

Conclusion: A favourable response rate could be achieved in malignant mesothelioma with ifosfamide, mesna and IFN combinaton therapy.

161 POSTER

Mesothelioma - a new therapeutical approach with Tomudex

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Purpose: Prior experiments showed a missing uptake of *H-thymidine but not of *H-thymidinemonophosphate into the nucleus of mesothelioma cells and suggested a diminished activity of the enzyme converting thymidine to thymidinmonophosphate, the thymidine kinase.In order to get evidence and to evaluate a new treatment regimen we tested the effects of a drug blocking the activity of the enzyme providing thymidinemonophosphate by de novo synthesis, the thymidylate-synthetase tomudex alone and in in combination with thymidine and thymidinmonophosphate.

Methods: Established cell lines were tested in 96 multi-well plates with Tomudex 1ng/ml versus control without supplements in the culture medium with or without thymidine and thymidinemonophosphate ranging from a dose level 0-400μmol. Cell survival was evaluated by an MTT test.

Results: All tested mesothelioma cell lines, the renal cell carcinoma lines and the ovarian cancer cells were sensible to Tomudex at a dose level of 1ng/ml showing a cell survival of 20%. Thymidine showed toxic effects at a dose level of 100μmol and thymidinemonophosphate in a dose range of 50μmol. The toxic effects caused by tomudex could be completely antagonized in the mesothelioma cells by thymdinemonophosphate 4 μmol whereas thymidine antagonized about 80% at a dose level of 30-40μmol/ml. In the renal cell carcinoma cell lines and in ovarian cancer cells complete antagonism of tomudex effects was achieved with thymidine and thymidinemonophosphate 4 μmol.

Conclusion: Tomudex provides a therapeutical approach to mesothelioma. Antagonism of toxic effects caused by tomudex can be taken as a measure for thymidine kinase substrate affinity in the mesothelioma cells. The results suggests a low substrate affinity providing a possibility of preventing side effects without altering the therapeutical effect.

162 POSTER

Evaluation of response to chemotherapy in lung cancer patients: an interdisciplinary comparison using RECIST and WHO criteria (ATOM 004)

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Imaging based assessment of objective response of a tumor to an anticancer treatment is a critical issue in cancer patient management both in daily practice and in clinical trials. Still, a precise and reproducible assessment of the tumor size is usually difficult. In fact, the evaluation criteria, the technique used, and the observer's background and experience may affect the evaluation result. In this study, we evaluated different specialists dealing with assessment of response to chemotherapy. In particular, we addressed the impact of the observer's background and experience, and the technique used on the accuracy of the tumor measurement; the consistency of measures by WHO vs. RECIST criteria is also reported.

Briefly, 25 medical doctors and 5 medical students were asked to measure a set of 11 selected tumor images on serial chest CT scans from NSCLC patients treated with chemotherapy. In order to represent the different specialists actually involved in lung cancer patient management, the M.D. population included 5 radiologists, 5 thoracic surgeons, 5 radiation oncologists, 5 pulmonologists, and 5 medical oncologists from the staff of the local Hospital and the local Faculty of Medicine. The years since M.D. degree varied widely among the physicians, ranging from 3 to 33 years, as well as the observer's familiarity with tumor measurements. The observers were asked to identify 1) the longest diameter (RECIST, unidimensional evaluation), and 2) the longest diameter and its perpendicular diameter (WHO, bidimensional). The technique of measurement (i.e. ruler, paper, compasses) was left up to the observer. Four lesions were also evaluated using the loop of the tumorimeter. The measurements by the radiologists were used as reference values.

A preliminary comparison of RECIST and WHO criteria shows consistent overall response rates (correlation coefficient 0.79). In addition, there is no significant difference in the accuracy of measurements among the different disciplinary groups (p =0.0914, C.I. 95%). However, medical oncologists gave the most accurate evaluations. Familiarity with measuring tumor lesions as well as years since MD degree do not seem to correlate with the measurement accuracy.

163 POSTER

Resection of pulmonary nodules equal or less than 10mm in diameter by video-assisted thoracic surgery with CT-guided hook wire technique

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The aim of this study was to assess the experience with video-assisted thoracic surgery for the resection of small pulmonary nodules (equal or less than 10 mm in diameter).

This study included 27 patients. The mean age of the patients (14 men, 13 women) was 59 years (range, 44 to 74years). All nodules were detected by computed tomography but not by routine chest radiography. All nodules were located at a maximum of 3 cm from the visceral pleura. The injection of hook wire with the guide of computed tomography was done about 90 minutes before operation.

Video-assisted thoracic surgery was converted into thoracotomy in 6 patients, because of diffuse pleural adhesion in 5, inability to confirm localization of nodule due to dislocation of the hook in 1. The mean diameter of resected nodules was 6.9 mm (range, 4 to 10 mm). All patients underwent wide wedge resection of lung with endoscopic devices. The nodule was malignant lesion in 10 patients (37%) and benign in 17 patients (63%). The malignant lesions included primary lung adenocarcinoma in 8 and metastatic tumor in 2. Benign lesions included inflammatory fibrous nodule in 9, intrapulmonary lymphnode in 5, inflammatory pseudotumor in 1, anthoracosis in1, sarcoidosis in1. In 8 primary lung cancer patients, wide wedge resection was a final procedure in 6 with bronchioloalveolar carcinoma, right basal segmentectomy in 1 and right middle lobectomy in 1. There was no mortality and no pulmonary complication. The mean duration of postoperative drainage was 3.6 day (range, 1 to 7).

We concluded that resection of pulmonary nodule equal or less than 10mm in diameter by video-assisted thoracic surgery with CT-guided hook wire technique was seemed to be feasible.

Non-small cell lung cancer

164 POSTER

Cooperative role of telomerase activity and p16 expression in the prognosis of non-small cell lung cancer

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Telomerase activity and p16 expression can be considered as two of the most important molecular markers implicated in tumorigenesis. Our main aim was to study the cooperative role of both molecular alterations in the prognosis of patients surgically resected for non-small cell lung tumours.

We have determined telomerase activity and p16 expression in a series of 98 prospectively collected non-small cell lung tumours obtained from patients who had suffered only surgery. Telomerase activity was investigated by a TRAP-ELISA based procedure, and p16 expression by Western-blot followed by promoter hypermethylation analysis in cases showing lack of p16 expression. Associations with survival were evaluated.

Positive results for telomerase activity were found in 82% of the cases, this variable being correlated with poor differentiation and recurrence of tumours. Lack of p16 expression was observed in 61% of tumours, 36% of which showed promoter hypermethylation. By univariate analysis, both negative telomerase activity and p16 positive expression were significantly correlated with a better prognosis of patients. Moreover, statistics for equality of survival distributions for telomerase, adjusted for p16, resulted significant by Breslow test (P = 0.03). These results indicated a positive interaction between the two parameters evaluated in this work, telomerase activity and p16 expression. For telomerase positive tumours, p16 expression emerged as a significant protective variable, independent of tumour stage, as indicated by Cox multivariate analysis (Relative Risk, RR = 0.214; P = 0.014).

These results suggest that the combined telomerase activity and p16 expression analyses may be considered of prognostic importance in non-small cell lung cancer.

165 POSTER

A randomized phase III trial of docetaxel (D) and cisplatin (P) versus vindesine (V) and p in stage IV non small cell lung cancer (NSCLC)

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Purpose: The purposes of this randomized study were to compare the survival, anti-tumor response and tolerability between DP and VP, Japanese standard regimen as of 1998, in patients with untreated stage IV NSCLC.

Methods: Eligible patients (pts) had measurable disease, adequate organ function and ECOG PS 0-2. Pts with PS 3 due to pain from bone metastasis or pts with asymptomatic brain metastasis were included in this study. DP consisted of P 80mg/m2 (day 1) and D 60mg/m2 (day 1), repeated every 3-4 weeks. No prophylactic steroid for edema was administered. VP consist of P 80mg/m2 (day 1) and V 3mg/m2 (day 1, 8, 15), repeated every 4 weeks. Crossover administration of D and V was prohibited for both treatment groups.

Results: Among 311 pts enrolled from 4/98 to 3/00 of whom 302 pts were assessable. 151 pts received DP and 151 pts received VP. Patient characteristics were; [DP arm] median age 63(30-74), median PS 1(0-3), histology (Adeno/Squamous/Other) 120/17/14, male/female 97/54, median delivered cycles 3(1-9), [VP arm] median age 64(39-74), median PS 1(0-3), histology (Adeno/Squamous/Other) 103/33/15, male/female 103/48, median delivered cycles 2(1-5).

Median survival times (MST) were 11.3 months vs. 9.6 months and 1-year survival rates were 48% vs. 43% for DP arm and VP arm, respectively. Response rate (RR) were 37% (56/151) for DP arm and 21% (32/151) for VP arm ($p<0.01$). Toxicity was assessed by NCI-CTC scale. Severe hematological toxicities were developed with similar profiles. (Grade 3-4 toxicity, DP arm; leukopenia 46%, neutropenia 75%, thrombocytopenia 1%: VP arm; leukopenia 68%, neutropenia 78%, thrombocytopenia 0%). On severe (grade3-4) non-hematological toxicity, diarrhea was observed higher in DP arm (9% vs. 1% $P<0.01$). Severe edema was not observed and other severe toxicities were rare in both arms.

Conclusion: Although both regimens were well tolerated, DP arm shows a significantly higher RR and shows better MST and 1-year survival rate than VP arm. DP combination chemotherapy should make one of the new standard regimens against NSCLC. Updated data will be presented at the meeting. Supported by Aventis Pharma Japan.

166 POSTER

Early prediction of response in patients with NSCLC stage III and IV during platin based chemotherapy by FDG-PET

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Rationale: This study was done to detect early after one cycle of platin based chemotherapy patients responding or not responding to chemotherapy.

Patients and Methods: 29 patients (6 f, 23 m, age: 61 ± 8 years) with histopathologically proven NSCLC stage III and IV underwent 2 to 8 cycles of platin based chemotherapy. A dynamic FDG-PET (injection of 300–400 MBq F-18-FDG) was performed prior to and three weeks after one cycle of chemotherapy (CTX). The chemotherapy used was cisplatin/vinorelbine (10), carboplatin/taxol (15), cisplatin/taxotere (3) and cisplatin/etoposide (1). Quantitative measurements of tumor FDG uptake were correlated with radiologically response after 2 cycles CTX measured with CT scan in accordance to WHO criteria. FDG uptake was quantitatively assessed by standardized uptake values (SUV, measured 40–60 min p.i.).

Results: Radiological response was 0/30 complete response, 11/30 partial responses, 10/30 stable diseases and 8 progressive diseases after 2 cycles of CTX. There was no significant correlation between the absolute FDG-uptake prior to CTX or after 1 cycle of CTX with the later response. But there was a significant correlation between the decrease of SUV and subsequent response ($p < 0.0001$) using a cut-off value of 18% reduction of FDG uptake. In responders FDG uptake decreased by 44% ± 15% while in non-responders the decrease was only 7% ± 21%. Response was predicted with a sensitivity of 100% and a specificity of 89%.

Conclusion: With FDG-PET a later response to CTX can be predicted very early with a high accuracy. The early detection of useless CTX can save side effects in non-responding patients. Furthermore the CTX can be modified early to a possible effective CTX to preserve the patients quality of life.

167 POSTER

A phase II study of LY355703 (cryptophycine) as first-line therapy for stage IIIb or IV NSCLC subjects: preliminary analysis

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Introduction: LY355703 (Cryptophycine-52) is a synthetic analogue derived from blue-green algae that inhibits microtubule dynamics. In phase I studies, one patient with NSCLC previously treated with taxanes achieved a PR lasting 4 months.

Purpose: The primary objective was to determine the objective response rate (CR or PR) The secondary objectives were 1) characterize the nature of toxicity; 2) measure time-to-event efficacy variables; and 3) characterize pharmacokinetics and identify potential factors that may influence LY355703 disposition in cancer subjects.

Patients & Methods: The trial involved two stages, with 18 patients enrolled in first stage. If at least 2 subjects responded to LY355703 therapy another 22 patients would be enrolled into the second stage. Since May 2000, 14 patients (12 male, 2 female with a median age of 58 yrs, range 41 - 70 yrs, all stage IV and WHO Performance Status of 0 or 1) received LY355703 1,5 mg/m2 iv over 2 h on days 1 and 8 of a 21-day-cycle following prophylactic hypersensitivity therapy. Two patients are currently ongoing in the study and are not included in this abstract.

Results: Fourteen patients received a total of 24 cycles; of these, 7 patients received 1 cycle, 5(2), 1(3), 1(4). No objective tumor responses were observed. Reasons for discontinuation included lack of efficacy (9 patients) and adverse events (3 Patients). Two patients died on study. One was hospitalized for Grade 4 diarrhoea and died from severe lactat acidosis possibly related to LY355703. The other patient suffered a myocardial infarction and died. Haematological toxicities were not observed. Other toxicities experienced were alopecia, constipation, fatigue, myalgia, arthralgia, neuropathy, tumor pain and hypertension. Two patients had acute hypersensitivity reactions (Grade 2) despite prophylaxis.

Conclusions: The trial has been suspended pending the result of the 2 ongoing patients and other ongoing phase II LY355703 trials. Supported by grant from Eli Lilly and Company.