Results: Out of eight eligible trials, one was available only in abstract form and did not report on ILD events. Five trials (4,932 patients, 2,530 gefitinib, 694 erlotinib, 1,708 placebo) were included in the TKI-placebo comparison. Four trials (1,829 patients) comparing two gefitinib doses (250 mg; 909 patients versus 500 mg; 920 patients) were included in the dose effect analysis. We found no evidence of a relationship between TKI treatment and ILD (OR, 1.09; 95% CI, 0.59 to 2.02). This held true when we analyzed erlotinib (OR, 1.14; 95% CI, 0.31 to 4.13) and gefitinib (OR, 1.08; 95% CI, 0.54 to 2.16) trials separately. TKIs were unrelated to ILD, both when given as monotherapy (OR, 0.77; 95% CI, 0.33 to 1.80) or in combination with cytotoxic agents (OR, 1.59; 95% CI, 0.66 to 3.86). We found no evidence of a dose effect relationship (OR, 0.88; 95% CI, 0.33 to 2.34) when comparing the two gefitinib doses regarding ILD incidence. Sensitivity analyses revealed no inconsistencies between different calculation methods.
Conclusion: We found no evidence of increased incidence of ILD events in patients receiving TKIs for advanced NSCLC, when compared to patients receiving placebo. Our observation is strengthened by the lack of a dose effect relationship between gefitinib administration and ILD development. Further study of ILD in NSCLC patients is warranted since there seems to be little evidence in support of the widely held belief in a causal relationship between TKI treatment and ILD.

6579 POSTER

Randomized phase II trial of irinotecan combined with paclitaxel or gemcitabine in untreated advanced non-small cell lung cancer

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Purpose: Patients with advanced non-small cell lung cancer (NSCLC) do not always tolerate cisplatin-based regimens because of its non-hematological toxicities. Given the activity and tolerability of irinotecan-containing regimens in NSCLC, a randomized phase II trial was conducted to evaluate the effects of irinotecan plus paclitaxel or gemcitabine in patients with previously untreated stage IIIB or IV NSCLC.
Patients and Methods: Patients with adequate organ functions, who gave their written informed consent to take part in this clinical trial, were randomly assigned to irinotecan 50 mg/m^2 on days 1, 8, and 15 plus paclitaxel 180 mg/m^2 on day 1 every 4 weeks (arm A) or irinotecan 100 mg/m^2 on days 1 and 8 plus gemcitabine 1000 mg/m^2 on days 1 and 8 every 3 weeks (arm B). The primary end point was response rate.
Results: From January 2004 to April 2006, a total of 80 Japanese patients were enrolled and 78 of them were assessable (38 in arm A and 40 in arm B). Baseline characteristics were comparable. Response rates were 31.6% (95% CI, 17.5 to 48.7) in arm A and 20.0% (95% CI, 9.1 to 35.6) in arm B, respectively. Median time to failure was 86 days in arm A and 145 days in arm B, respectively. Adverse events profiles were, as expected in both arms, no significant additives. The most common grade 3 or 4 adverse events were neutropenia, (78.9% in arm A and 50.0% in arm B).
Conclusion: Both arms are well tolerated in NSCLC patients. In terms of the response rate, irinotecan plus paclitaxel (arm A) may be useful in patients not suitable for cisplatin.

6580 POSTER

Value of lung perfusion in stage III non-small cell lung cancer patients treated with radiotherapy

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Background: To study the value of lung perfusion single photon emission computed tomography (SPECT) scans for patients with stage III non-small cell lung cancer (NSCLC) treated with radiotherapy (RT).
Materials and Methods: 15 patients with stage III NSCLC treated with RT were enrolled. All patients had PET-CT and SPECT scans. The imagings were accurately co-registered in the treatment planning system. The PET-CT images were used to define the gross tumor volume where the standardized uptake value (SUV) > 2.5 was used as the threshold. The SPECT images were used to define the volume of perfused functional lung (FL) and non-functional lung (NFL). FL refers to the region of $\geqslant$30% maximum radioactive counts and the others were categorized as NFL. The degrees of lung perfusion deficit were classified by comparing lung perfusion damaging with area of radiological abnormality as followings. Grade 0: no lung perfusion deficit; Grade 1: the size of radiological abnormality is similar to the area of lung perfusion deficit; Grade 2: the area of lung perfusion is bigger than that of radiological abnormality, and extend to 1 pulmonary lobe; Grade 3: the area of lung perfusion deficit exceed 1 pulmonary lobe. Three dimensional conformal radiotherapy (3DCRT) plans were optimized before lung perfusion. After lung perfusion, to minimize the dose to FL both CT-PET and SPECT lung perfusion imagings were used to optimize 3DCRT and intensity modulation radiotherapy (IMRT) plans. Randomized block analysis of variance was used to analyze the difference of the percentage of whole lung volume received dose $\geqslant$xGy (WLVx) and the percentage of functional lung volume received dose $\geqslant$xGy (FLVx) among the three sets of treatment plans.
Results: All patients had different lung perfusion deficits. Among them 7 patients had grade 1 damage, 4 patients grade 2 damage, and 4 patient grade 3 damage. After the optimization of radiotherapy plans using SPECT perfusion imaging, WLVx and FLVx were decreased significantly both in the 3DCRT plan and in the IMRT plan. Comparing with plans without lung perfusion imaging, there were significant differences in WLV10, WLV15, WLV20, WLV25 ($p < 0.05$) and FLV10, FLV15, FLV20, FLV25 ($p < 0.05$) after the treatment planning was optimized with SPECT imaging. However, there was no significant difference in WLV10, WLV15, WLV20, WLV25 ($P > 0.05$)and FLV10, FLV15, FLV20, FLV25 ($P > 0.05$)between 3DCRT and IMRT arms. When the lung tumor had irregular shape or located in chest wall, IMRT planning had more ascendant than 3DCRT planning. For patients with large perfusion deficits away from lung tumor, the WLVx and FLVx decreased more significantly.
Conclusions: SPECT lung perfusion images were helpful in sparing FL for stage III NSCLC patients treated with RT, especially for ones with large perfusion deficits.

6581 POSTER

Assessment of maintenance oral etopside following induction chemotherapy with gemcitabine and cisplatin in chemo-naive extensive small cell lung cancer patients

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Background: Although vepsid-cisplatin combination is considered the standard treatment for extensive disease SCLC patients yet the majority of patients will relapse with poor long term outcome. So we try the use of gemcitabine-cisplatin combination to evaluate the response and tolerability to treatment, followed by maintenance therapy of oral etopside for non-progressive patients in trial to improve progression free survival and overall survival.
Patients and Methods: Thirty nine patients with extensive SCLC and ECOG $\leqslant$2, were enrolled to receive 4 cycles of chemotherapy consisting of gemcitabine 1000 mg/m^2 (day 1 and 8) and cisplatin 80 mg/m^2 (day 1) every three weeks. Twenty seven non-progressive patients after 4 cycles of chemotherapy were randomized either to receive oral etopside 50 mg/m^2 for consecutive 15days every 3 weeks vs. no therapy until progression.
Results: From January 2003 to September 2005, 39 patients treated with GC, 27 non progressive patients were subsequently randomized to oral etopside (N = 14) or observation (N = 13). Minimum follow up was 18 months. The overall response rate to GC was 59% and toxicity to oral etopside was mild. There was improvement if median PFS favoring the maintenance arm of 10.5 months vs. 7 months ($P < 0.05$). Median OS is improving towards the maintenance arm (13 Vs. 11.5 months). One year survival (60% vs. 24%), 18 months survival (20% vs. 5%) favoring the maintenance. Multivariate analysis revealed that age, performance status, maintenance therapy, and response to treatment were independent prognostic factors for OS ($P < 0.01$) meanwhile age, maintenance therapy, and response to treatment are highly significant factors for PFS ($P < 0.001$).
Conclusion: gemcitabine-cisplatin is an effective and tolerable regiment for extensive disease of SCLC. The addition of 3 months of oral etopside in non progressing patients was associated with a significant improvement of both PFS and OS.

6582 POSTER

Oral vinorelbine concomitantly with thoracic radiotherapy (RT) in locally-advanced or inoperable stage III non-small cell lung cancer (NSCLC): interim results of a phase I dose escalation trial

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Background: In vitro, vinorelbine (NVB) has shown to be a powerful radiosensitizer. The intravenous (IV) formulation led to an encouraging response rate of 75% at a daily dose of 4 mg/m^2 concurrently with 55 Gy

RT in 8 patients who completed the planned treatment (C. Gridelli, Lung Cancer 2000); the Maximum Tolerated Dose (MTD) was 5 mg/m^2/day.
Oral vinorelbine (NVBo) has produced similar results in advanced NSCLC when compared to IV NVB. Based on the bioavailability of NVBo (40%) and the available marketed dosages (20−30 mg), a feasibility study has been implemented in patients (pts) with locally advanced or inoperable stage III NSCLC.
Material and Methods: Three to 6 pts between 18 and 70 years, with histologically proven untreated locally advanced inoperable stage IIIAN2/IIIB (supraclavicular lymph nodes and pleural effusion excluded) NSCLC, adequate bone marrow, hepatic and renal function, KPS $\geqslant$ 80%, were expected at each dose level. Eight levels were planned with NVBo given concomitantly with 60 Gy RT (2 Gy/day; 5 days a week) from 20 mg total dose up to 60 mg total dose on days (D) 1, 3 and 5 each week during 6 weeks. Here we report the analysis of the first 5 dose levels.
Results: Between 06/02 and 07/06, 12 men and 3 women were enrolled with stages IIIA N2 (2 pts) or IIIB (13 pts). Median age 61.2 years [49.3−71.3], median KPS 100% [80–100%]. The first 5 levels were completed without the occurrence of dose-limiting toxicity (3 pts per dose level). Overall, 11 pts received 100% of the planned NVBo dose during the 6 weeks treatment period and 4 pts missed only one intake for other reason than toxicity.
Neither grade $\geqslant$3 haematological/ non-haematological toxicity nor treatment interruption >2 weeks occured. Only 2 pts experienced grade 2 radiation-induced oesophagitis and constipation. Objective response was observed in 4 pts (27%) and 2 additional pts had confirmed partial response during follow-up.
Conclusion: NVBo with this new original schedule of 3 times a week intake concomitantly with RT for 6 weeks, is still well tolerated with dosages up to 50 mg on D1, 40 mg D3 and 40 mg D5, each week, without MTD. Additional dose escalation is ongoing to determine the recommended dose for phase II trials.

6583 POSTER

The prognostic value of hemoglobin concentration and WBC count in sequential radio-chemotherapy or radiotherapy alone for locally advanced non-small cell lung cancer

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Background: The aim of this study was to evaluate the prognostic value of hemoglobin concentration at the beginning (Hb1) and at the end (Hb2) of sequential radio-chemotherapy or radiotherapy alone for lung cancer. The analysis accounted for WBC count, platelets count, as well as tumor and treatment related variables.
Material and Methods: The retrospective study included 224 patients treated between 1998 and 2003 for stage IIIB non-small cell lung cancer: 118 patients received cisplatine-based induction chemotherapy (2−6 cycles) followed by conventionally fractionated 3-D conformal radiotherapy (median total dose 66 Gy, dose per fraction 2.0 Gy), while 106 patients were treated with radiotherapy alone (median dose 66 Gy). The variables used in the analysis included Hb, WBC and platelets counts at the beginning and at the end of radiotherapy, as well as 8 tumor and treatment related variables (general performance status, age, sex, TN stage, number of chemotherapy cycles, total radiation dose, overall radiation treatment time). A multivariate Cox proportional hazard regression analysis was performed to identify the variables that significantly affected overall survival (OS). Backward stepwise regression was used to optimize the model.
Results: Several of the parameters studied (e.g. platelets count, $p = 0.02$) appeared to have a significant influence on OS of 224 patients when univariate model was used, but only Hb2 remained significant ($p < 0.00001$) in a multivariate model. Likewise, only Hb2 appeared significant ($p = 0.00004$) when multivariate analysis was restricted to subgroup of the patients treated with radiotherapy alone. By contrast, not only low Hb2, but also the above-average WBC count at the end of radiotherapy (WBC2), low number of chemotherapy courses, and advanced N stage appeared as significant and independent predictor of impaired OS among the patients treated with radio-chemotherapy.
Conclusion: Hemoglobin concentration at the end of radiation treatment appear to be the strongest predictor of long-term survival among the patients with non-small cell lung cancer treated with radiotherapy alone. In patients treated with induction chemotherapy the above-average WBC count at the end of radiotherapy was also a predictor of an impaired survival. This may suggest that the above-average WBC2 may be considered as one of the surrogate markers of individual resistance to cytotoxic therapy, and/or a sign of a deficient systemic treatment.

6584 POSTER

Induction chemotherapy with vinorelbine and a platinum compound followed by concurrent chemoradiotherapy and consolidation chemotherapy with the same drugs for stage III non-small-cell lung cancer (NSCLC) – a phase II study

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Purpose: to determine the response rate (RR), toxicity, time to progression (TTP) and survival (S) of induction Chemotherapy (ChT) with Vinorelbine (Vrb) and Cisplatin (Cis) or Carboplatin (Carbo) followed by concurrent chemoradiotherapy (ChRT) and consolidation ChT with the same drugs, for stage III NSCLC.
Methods and Materials: 53 patients (pts) were included from 05.02.2004 to 20.12.2006: median age 57(39–73), M/F=50/3, PS 1/2=31/22, stage IIIA/IIIB=6/47, squamous cell cc 43, large cell cc 5, adenocc 1, "non-small" carcinoma 4. Treatment consisted of 2 cycles (c) of induction ChT with Vrb (25 mg/sqm, d1, 8, q21) and Cis (100 mg/sqm, d1, q21), or Carbo (AUC 5, d1, q21), followed by 2 more c (with reduced doses: Vrb 15 mg/sqm, d1, 8, q21, Cis 80 mg/sqm, d1, q21 or Carbo AUC 2.5, d1, q21) given concurrently with RT and 2 c of consolidation ChT with the same drugs. RT (15MV) has been administrated to a total dose of 60−68 Gy/30−34 fractions. The last 17 pts benefited of conformal-3DRT. 86% of pts completed at least 4 c, 70% completed 5 or 6 c of ChT. The optimal doses of RT have been received by 75% of pts.
Results: 53 pts were evaluable for toxicity. Severe grade (gr) 3 or 4 neutropenia occured in 5 pts, anemia in 4.One pt had gr 3 trombocitopenia and also 2 pts had gr 3 gastro-intestinal toxicity. Gr 3 neuropathy occured in 1 pt.
Two pts stopped treatment after 2 c of induction ChT (one because of gr 3 neuropathy, gr 2 febrile neutropenia and evolution of the disease, and the other because of gr 4 neutropenia and decompensation of diabetes melitus). Other 2 pts didn't receive cycle 3 of chemotherapy because of toxicities or evolution of the disease. Of the 53 pts. evaluable after induction ChT, 5.7% obtained CR, 37.8% PR, 52.8% had SD and 3.7% PD. Of the 49 pts evaluable for response after ChRT, 33% achieved CR, 37% PR for an overall RR of 70% (CI:58−82), 18% of pts had SD, and 12% had PD.
Progression-free-S at 1 year was 38% (CI:24−53%) with a mTTP of 9 months (CI:6.9−17.9). The disease specific S at 1 year was 60% (CI:44%-73%) and the mS was not reached yet. For the 27 pts still alive the median follow-up was 9.6 months.
Conclusions: Preliminary results indicate that induction ChT followed by concurrent ChRT with Vrb and a Platinum compound, followed by consolidation ChT with the same drugs given for advanced stage III NSCLC is feasible, well tolerated and has a positive effect on the RR and survival

6585 POSTER

Accelerated radical radiotherapy for non-small cell lung cancer (NSCLC) using two common regimens: a single centre audit of outcome

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Background: Radical radiotherapy (RT) regimens for NSCLC vary considerably. Our centre uses both continuous hyperfractionated accelerated radiotherapy (CHART) and accelerated hypofractionated RT using 55 Gy in 20 fractions over 4 weeks. This audit reports outcome according to RT regimen.
Materials and Methods: All case notes and RT records of radically treated patients between 1999 and 2004 were retrospectively reviewed. Basic patient demographics, tumours, characteristics, RT and survival data were collected. Patients treated with CHART received 54 Gy in 36 fractions over 12 days.
Results: One hundred and thirty-seven patients received CHART and 140 received hypofractionated RT. Median age was 65 (41−83) in CHART and 73 (33−87) in hypofractionated group respectively. Sixty-five percent were male in CHART compared to 61% in hypofractionated group. Histological confirmation was obtained in 90% of CHART and 76% of hypofractionated patients. For CHART patients, stages 1, 2, 3 and unclassified were 12%, 8.0%, 68% and 12% and the staging for the hypofractionated regimen was 54%, 11%, 34%, 2% respectively. WHO performance status was 0/1, 2/3 and undocumented in 88%, 6%, and 7% of CHART patients and 78%, 22%, and 0% of the hypofractionated patients. Prior chemotherapy was given in 34% CHART and 19% of hypofractionated patients. Median overall survival (OS) from time of diagnosis was 16.6 months and 21.4 months in