B2-07 Cytotoxic Chemotherapy II, Tue, 13:45 - 15:30

Impact of 3rd generation drugs on the activity of first-line chemotherapy in advanced non-small cell lung cancer (NSCLC): a meta-analytical approach

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A two-drug platinum-based regimen with cisplatin or carboplatin combined with a third-generation agent gemcitabine (G), paclitaxel (P), vinorelbine (V), or docetaxel (D) is the standard first-line treatment for advanced NSCLC patients. Large clinical trials comparing various third-generation doublets showed similar efficacy.

The aim of this study is to assess the impact of G, P, V and D on the activity of first-line chemotherapy in advanced NSCLC, we carried out four separate meta-analyses on data from 6,671 NSCLC patients who were enrolled in 18 randomized trials comparing a G or P or V or D-containing vs. G or P or V or D-free regimens. We constructed 2x2 tables using response to treatment data. For trials with more than one eligible free comparator arm, individual comparisons between the G or P or V or D-based treatment arms and each of the comparator arms were analyzed. A general variance-based method was used to estimate the pooled odds ratio (OR) and 95% confidence interval (CI). We assessed for heterogeneity among the trials based on standard methods.

Seventeen, 9, 14 and 8 comparisons contributed to this analysis for G, P, V and D respectively. Comparing G-containing vs. G-free regimens, the OR for progression was 0.8633 (CI 95% 0.76-0.97; p=0.016); no significant difference was observed for overall (complete + partial) response (OR 0.96, CI 95% 0.84-1.10). The heterogeneity chi-square were 12.97 (p=0.60) and 19.53 (p=0.24), respectively. Comparing P-containing vs. P-free regimens, no significant difference was observed for overall response (OR 0.96, CI 95% 0.83-1.11) while P was estimated to be associated to an increased risk of progression (OR 1.21, CI 95% 1.06-1.38; p=0.0045). The heterogeneity chi-square were 5.20 (p=0.73) and 4.92 (p=0.76), respectively. Comparing V-containing vs. V-free regimens, no significant difference was observed for both overall response (OR 0.98, CI 95% 0.83-1.15) and for progression (OR 1.06, CI 95% 0.92-1.21). The heterogeneity chi-square were 20.73 (p=0.07) and 9.03 (p=0.69), respectively. Comparing D-containing vs. D-free regimens, the OR for progression was 0.9313 (CI 95% 0.81-1.06; p=0.28); no significant difference was observed for overall response (OR 0.95, CI 95% 0.77-1.17). The heterogeneity chi-square were 4.70 (p=0.69) and 14.25 (p=0.04), respectively.

These data demonstrate a similar probability to obtain an overall response between regimens. G containing regimens demonstrated a 14% reduction in the risk of an immediate progression. While P containing regimens were associated with a 21% increase in the risk of an immediate progression. Further analyses are required to address whether disease control is associated with a survival benefit and may therefore be used as a surrogate end point for survival in chemotherapy trials of NSCLC.

Session B3: Molecular Targeted Therapy: EGFR Inhibitors
Tuesday, September 4

B3-01 Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30

A randomized Phase III study to compare the overall survival of gefitinib (IRESSA) versus docetaxel in Japanese patients with previously treated advanced non-small-cell lung cancer

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Background: This prospective randomized, open-label, Phase III study (V-15-32) compared overall survival between gefitinib (250 mg/day) and docetaxel (60 mg/m^2) in pretreated patients with non-small-cell lung cancer (NSCLC).

Methods: Patients had advanced/metastatic NSCLC and had failed one/two chemotherapy regimens. Stratification factors for randomization were sex (female vs. male), performance status (0-1 vs. 2), histology (adenocarcinoma vs. others) and study site. Non-inferiority of the primary endpoint, overall survival, was assessed by the confidence interval (CI) of the gefitinib/docetaxel hazard ratio (HR) derived from an unadjusted Cox proportional hazards model. Secondary endpoints were progression free survival (PFS), time to treatment failure (TTF), objective response rate (ORR), disease control rate (DCR), quality of life (QoL; Functional Assessment of Cancer Therapy - Lung [FACT-L]), disease-related symptoms (FACT-L lung cancer subscale [LCS]), and safety. Exploratory endpoints included biomarker expression in tumor tissue and potential correlation with outcome.

Results: Between September 2003 and January 2006, 489 eligible patients (62% male, 78% adenocarcinoma, 32% never-smokers) were recruited from 50 institutes. Treatment arms were generally well balanced for baseline demographics. Non-inferiority in overall survival was not achieved (HR 1.12; 95.24% CI 0.89, 1.40) according to the predefined criterion (upper CI limit for HR <1.25), however, no significant difference in overall survival was apparent between the treatment groups (p=0.330). Median survival times were 11.5 (gefitinib) and 14.0 (docetaxel) months. Post-study, 36% of gefitinib-treated patients received subsequent docetaxel and 40% received no other therapy apart from gefitinib; 53% of docetaxel-treated patients received subsequent gefitinib and 26% received no other therapy apart from docetaxel. Gefitinib significantly improved ORR (22.5% vs. 12.8%; p=0.009), TTF (HR 0.63; 95% CI 0.51, 0.77; p<0.001) and QoL improvement rates (FACT-L trial outcome index 20.5% vs. 8.7%; p=0.002; FACT-L 23.4% vs. 13.9%; p=0.023), compared with docetaxel. No significant differences between treatments were seen in PFS (HR 0.90; 95% CI 0.72, 1.12; p=0.335), DCR (34.0% vs. 33.2%; p=0.735) or LCS improvement rates (22.7% vs. 20.4%; p=0.562). Adverse events (AEs) were consistent with those previously seen with gefitinib and docetaxel.

Grade 3/4 AEs occurred in 40.6% (gefitinib) and 81.6% (docetaxel) of patients. The incidence of interstitial lung disease (ILD) was 5.7% (n=14) and 2.9% (n=7) with gefitinib and docetaxel, respectively. There were four deaths due to AEs in the gefitinib arm (three possibly treatment-related due to ILD; one due to pneumonia that was not considered treatment-related), and none in the docetaxel arm. Biomarker data will also be reported.

Conclusions: Non-inferiority in overall survival between gefitinib and docetaxel was not demonstrated according to predefined criteria. However, there was no statistically significant difference in survival between the two groups. Imbalances in the proportion and type of post-study treatments in both arms have complicated interpretation of survival results. The secondary endpoints are largely unaffected by subsequent therapy and provide further evidence of the clinical efficacy of gefitinib in Japanese patients. AEs were consistent with those previously observed for both treatments.

B3-02 Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30

Randomized, double-blind, multicenter, parallel-group, Phase II study of gefitinib (IRESSA) plus best supportive care (BSC) versus placebo plus BSC in chemotherapy-naïve patients with advanced non-small-cell lung cancer and poor performance status (INSTEP)

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Background: It is estimated that 30-40% of patients with advanced non-small-cell lung cancer (NSCLC) have a poor performance status (PS); however, there is no consensus on the best treatment approach for such patients (Gridelli et al, Ann Oncol 2004;15:419-426). In a large randomized four arm, Phase III study, the median survival for PS2 patients treated with combination chemotherapy was 3.9 months (Schiller et al, NEJM 2002;346:92-98). Single-agent chemotherapy is also an option for PS2 patients (Gridelli et al, Lung Cancer 2002;38: S37-S41) but there is a need for effective treatment alternatives for patients considered unfit for chemotherapy or who refuse chemotherapy. A retrospective review of 198 chemotherapy-naïve patients (20% PS2 and 3) with advanced NSCLC who received gefitinib (IRESSA) within a compassionate use program in the USA, reported a median survival of 6 months and objective response rate of 6.3% (Govindan et al. Lung Cancer 2006;53:331-337). The Phase II, randomized, double-blind, multicenter, parallel-group study reported here compared gefitinib plus BSC to placebo plus BSC in patients with advanced NSCLC and poor PS (IRESSA NSCLC Trial Evaluating Poor PS patients [INSTEP]).

Methods: This study planned to recruit approximately 200 patients. Following written, informed consent, patients (≥18 years) with locally advanced or metastatic (stage IIIB or IV) NSCLC who were chemotherapy-naïve, had a poor PS (WHO PS 2 or 3) and were considered unfit for chemotherapy were randomized to gefitinib (250 mg/day orally) plus BSC or placebo plus BSC. The primary objective of this study was to compare progression-free survival (PFS) between the two treatment groups. Secondary endpoints were objective response rate (assessed every 6 weeks using RECIST criteria), overall survival, patient-reported functionality and quality of life (via the Functional Assessment of Cancer Therapy-Lung [FACT-L] trial outcome index and total score, respectively), pulmonary symptom improvement (as measured by the pulmonary items of the FACT-L lung cancer subscale), and tolerability (frequency and severity of adverse events [via CTC version 3.0] and laboratory parameters). An exploratory endpoint was to correlate the efficacy of gefitinib with epidermal growth factor receptor (EGFR) gene copy number. A proportional hazards model (presenting a hazard ratio and its associated 95% confidence intervals) will be used to compare PFS between treatment groups, with gender, PS, histology, smoking history, and stage as covariates. While median PFS on BSC is expected to be in the region of 4 weeks, there are no data upon which to accurately anticipate the effectiveness of gefitinib in this setting. With 200 patients recruited, this study would have greater than 90% power to detect a 75% improvement in PFS and 81% power to detect a 50% improvement in PFS.

Results: Between September 2004 and December 2006, 201 patients were randomized from 5 countries and 37 centers. Efficacy, quality of life, safety and EGFR gene copy number results will be available for presentation at this meeting.

Conclusions: To be completed once data are available.

IRESSA is a trademark of the AstraZeneca group of companies

B3-03 Molecular Targeted Therapy: EGFR Inhibitors, Tue, 13:45 - 15:30

A randomized multicenter phase III study of cetuximab (Erbitux®) in combination with Taxane/Carboplatin versus Taxane/Carboplatin alone as first-line treatment for patients with advanced/metastatic Non-small cell lung cancer (NSCLC)

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Background: Cetuximab (Erbitux®) is a chimeric monoclonal IgG1 antibody targeting the epidermal growth factor receptor (EGFR) thereby blocking ligand-receptor interaction, promoting receptor internalization, cell cycle arrest and apoptosis. Several phase II studies with cetuximab in combination with platinum based chemotherapy have shown encouraging anti-tumor activity in patients with advanced/metastatic NSCLC. This randomized phase III study was conducted to determine the efficacy of adding cetuximab to taxane/platinum chemotherapy in patients with recurrent or metastatic NSCLC in a randomized controlled setting.

Methods: Patients with previously untreated stage IIIB (malignant pleural effusion) or stage IV NSCLC were eligible for this study. Patients on arm A received cetuximab (400 mg/m^2 IV on day 1 followed by 250 mg/m^2 weekly) combined with either paclitaxel (225 mg/m^2 IV q3 weeks) or docetaxel (75mg mg/m^2 IV q3 weeks) and carboplatin (AUC 6 IV q3 weeks). Patients on Arm B received the same chemo-