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Favorable benefit to risk profile for pemetrexed plus cisplatin versus gemcitabine plus cisplatin in a large phase III study of first-line therapy in advanced non-small cell lung cancer

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Background: In a recently concluded large phase III study, chemonaive patients with stage IIIB/IV non-small cell lung cancer (NSCLC) who were treated with pemetrexed plus cisplatin (PC) had similar efficacy with better tolerability and more convenient administration than patients who received gemcitabine plus cisplatin (GC). Overall survival for patients treated with PC was non-inferior to those on GC (HR 0.94, 95% CI 0.84−1.05) with the entire 95% CI well below the 1.176 non-inferiority margin.
Methods: In the aforementioned study, survival without grade 4 toxicity was defined (for all randomized patients receiving study treatment) as the time to the first occurrence of CTC grade 4 toxicity or death, analyzed using Kaplan-Meier and Cox methods. This prospectively defined analysis is a measure of benefit relative to risk in that overall survival time (ie, clinical benefit) relative to the first occurrence of CTC grade 4 toxicity (ie, clinical risk) was compared between treatments. A similar additional analysis also included grade 3 toxicities. The phase III study randomized 1725 patients to receive PC (P 500 mg/m^2 d1; C 75 mg/m^2 d1) or GC (G 1250 mg/m^2 d1, 8; C 75 mg/m^2 d1) every 3 weeks for up to 6 cycles. Both arms received dexamethasone prophylaxis, folic acid and vitamin B_{12} supplementation. Patients had previously untreated stage IIIB (24%) or IV (76%) NSCLC and an ECOG PS of 0−1 (37%/63%).
Results: 839 pts receiving PC and 830 pts receiving GC were included in these analyses. Baseline characteristics and known prognostic factors were well balanced across treatment arms. PC demonstrated a statistically significantly longer survival without grade 4 toxicity compared with GC (HR = 0.83; 95% CI = 0.74−0.92, p < 0.001); with a median time of 9.0 vs 7.3 mos. PC also demonstrated statistically longer survival without grade 3/4 toxicity compared with GC (HR = 0.82, 95% CI = 0.74−0.91 p < 0.001); with a median time of 1.6 vs 1.1 mos.
Conclusion: This analysis of survival without grade 4 toxicity or without grade 3/4 toxicity shows a statistically significant advantage for PC over GC and suggests a benefit-to-risk profile that favors PC over GC in first-line treatment of patients with NSCLC. This analysis helps to further characterize PC as a favorable treatment option in this setting.

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Multi-gene prediction of distant relapse-free survival in early NSCLC: microarray expression-profiling study

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Background: The aim of the study was to obtain a prognostic multi-gene classifier for relapse-free survival in stage I-II NSCLC, in the context of lymph node status as an established prognostic factor.
Materials and Methods: Tumor specimens were collected from 70 NSCLC patients (pts) who underwent curative pulmonary resection between 1999 and 2004 in two Polish centers (Gdansk, Bialystok). There were 54 men and 16 women aged 37−77 yrs (median 62.5 yrs), 45 with squamous cell ca, 22 with adenoca and 3 with large cell ca. Eight pts were staged pT1, 59 pT2 and 3 pT3; there were 49 and 21 pN0 and pN1 pts, respectively. 30 pts had a relapse and 32 pts died (median follow-up 36 months). Samples of tumor tissue were collected intraoperatively and snap-frozen, total RNA was isolated by phenol-chlorophorm extraction followed by RNeasy on-column purification. The transcriptome of lung cancer specimens was analyzed by gene expression profiling (Affymetrix HG-U133 2.0 Plus oligonucleotide microarray). Class prediction was carried out by Support Vector Machines and Bayesian Compound Covariate Classifier, using own procedures and BRB-Array software developed by Simon and Peng Lam. Survival time prediction was carried out by method developed by Bair and Tibshirani (PLoS Biology 2004).
Results: The optimal classifier predictive for relapse, obtained by cross-validation of 70-sample dataset, consisted of 170 transcripts selected by univariate p-value 0.001. In this set, the relapse could be predicted with 75.0% specificity and 53.3% sensitivity (positive predictive value [PPV] 61.5%, negative predictive value [NPV] 68.2%) using Bayesian Compound Covariate method. When the cross-validated prediction was carried out within N1 group of patients, we obtained good sensitivity (73.3%), but poor specificity of the method (33.3%, PPV 64.7%, NPV 42.9%). When N1 group was used to test the relapse predictor obtained within N0 patients, 12 of 21 patients (57.1%) were correctly predicted, much worse than 69% accuracy obtained by cross-validation within N0 dataset.
Further gene selection was based on the prediction of the relapse-free survival time: 1919 genes, obtained by fitting Cox proportional hazard model (p < 0.05) and further used to predict survival by 4 principal components, distinguished between pts with high and low risk of relapse (p < 0.05, log-rank test). For final gene selection, nodal status was included within the model.
Conclusions: Prediction of the risk of relapse in stage I-II NSCLC based on the gene expression profile is feasible, with NPV of 68.2%.
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Poster presentations (Mon, 24 Sep, 09:00−12:00)
Lung cancer

6521 POSTER

Is pemetrexed more effective in patients with non-squamous histology? A retrospective analysis of a phase III trial of pemetrexed vs docetaxel in previously treated patients with advanced non-small cell lung cancer (NSCLC)

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Background: Pemetrexed (a multitargeted antifolate and potent TS inhibitor) compared favorably (with similar efficacy and lower toxicity) to docetaxel in a large, randomized phase III trial of previously treated patients with NSCLC. Preclinical data indicates that overexpression of TS correlates with reduced sensitivity to pemetrexed in antifolate-resistant cell lines. A recent study on chemonaive NSCLC patients indicated higher TS expression levels found in squamous cell carcinoma. These data suggest the possibility of improved efficacy for pemetrexed among patients with non-squamous histology.
Methods: This is a retrospective analysis of the large phase III study of pemetrexed (500 mg/m^2 IV with vitamin B_{12} injections + oral folic acid), vs docetaxel (75 mg/m^2 IV) Q 21 days. This analysis assesses whether the efficacy of pemetrexed is higher in patients with non-squamous histology. A Cox model of overall survival (OS) was used to test for a significant treatment-by-histology interaction, and subsequent Cox models were used to estimate hazard ratios (HR) for OS and progression-free survival (PFS) in both squamous and non-squamous groups. All models included baseline cofactors for performance status (ECOG PS), time since prior chemotherapy (TSPC), disease stage, and gender. Medians for OS and PFS were derived by the Kaplan-Meier method.
Results: Treatment-by-histology interaction was statistically significant (p = 0.001), indicating that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others on trial. The table summarizes results by group.
Conclusions: The statistically significant treatment-by-histology interaction indicates that patients with non-squamous histology treated with pemetrexed had higher survival compared to all others on trial. Efficacy with docetaxel did not differ greatly between squamous and non-squamous