

Indirect Comparison of Pemetrexed plus Cisplatin with Other Platinum-based Therapies for First-line Advanced Non-small Cell Lung Cancer

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Background

A recent randomized, phase III trial compared pemetrexed plus cisplatin (pem/cis) with gemcitabine plus cisplatin (gem/cis) as first-line therapy for advanced non-small cell lung cancer (NSCLC) (Scagliotti et al, J Clin Oncol 2008). Randomized, head-to-head data are not currently available to compare pem/cis with other commonly used first-line regimens. In absence of these data, one must rely on indirect comparisons. One approach is to conduct indirect comparisons with a mixed treatment comparison that considers a network built from available relevant data. This methodology allows for retention of the benefits of randomization and consideration of relative rather than absolute differences between therapies.

Methods

The network for the mixed treatment comparison was built with doublet combinations of pem, docetaxel (doc), gem, paclitaxel (pac) or vinorelbine (vin) plus cisplatin or carboplatin (cb) and platinum triplets with bevacizumab (bev). Outcomes of interest were overall survival, one-year survival rate, time to progression (TtP), tumor response rate and select grade 3/4 toxicities. A systematic literature review was conducted in September 2007. Eligible studies included at least one of the regimens of interest, were randomized, and included patients with stage IIIB and/or IV disease who had not previously been treated with chemotherapy and had performance status ≤ 2 (or Karnofsky performance status ≥ 70). Literature included English-language manuscripts published 1995 to September 2007 and abstracts from 2006 to 2007 from ASCO and IASLC. Studies were excluded if patient eligibility included stage IIIA, elderly or poor performance status only, or where other treatment modalities than chemotherapy were evaluated. Data were extracted using a pre-specified template. Quality of studies were rated using the European Lung Cancer Working Party criteria. Updated results from secondary publications were used when available. Each outcome was analyzed independently, relative to pem/cis outcomes. Hazard ratios for overall survival and TtP were extracted and analyzed. Progression-free survival (PFS) was substituted when TtP was not reported. Odds ratios for rates of one-year survival, tumor response and toxicities were analyzed. When both nausea and vomiting were reported, the higher rate of the two was used in the analysis. Analyses were conducted with fixed effect and random effect modelling; the latter does not assume homogeneity across the studies. Sensitivity analyses included adjustments for distributions of disease stage, performance status, gender and histology. Further sensitivity analyses excluded studies based on publication year, sample size, age, histology restrictions (ie, bev), or quality score. Preliminary results are reported here.

Results

Twenty-six studies, including the pem/cis versus gem/cis study, were identified; this represented 12,944 patients. Of the 26 studies, overall survival was reported in 17, one-year survival rate in 23, TtP (or PFS) in 14, and tumor response rate in 26. Thrombocytopenia was reported in 26 studies,

neutropenia and anemia each in 24, nausea/vomiting in 23, febrile neutropenia in 16, and diarrhea in 13. Preliminary results with random effect modelling are reported. Hazard ratios for overall survival ranged from 1.04 to 2.07, with all 95% confidence intervals (CIs) including 1, but numerically favoring pem/cis. Hazard ratios for TtP ranged from 0.75 to 2.42, with all 95% CIs including 1; the majority of the hazard ratios were >1, numerically favoring pem/cis. Odds ratios for one-year survival ranged from 0.57 to 1.19, with all 95% CIs including 1. Odds ratios for tumor response ranged from 0.41 to 1.95, with nearly all 95% CIs including 1. Almost all 95% CIs for odds ratios for toxicities included 1, but with trends favoring pem/cis for neutropenia and febrile neutropenia and not favoring pem/cis for nausea/vomiting despite the low rate of 7%. Sensitivity analyses had little impact on results.

Conclusion

Using mixed treatment comparison, we were able to indirectly compare pem/cis to other common first-line regimens for NSCLC. Preliminary analyses of efficacy outcomes suggest that pem/cis is comparable to other first-line regimens in general NSCLC populations. Differences in toxicity were detected with trends favoring pem/cis for neutropenia and febrile neutropenia, but not favoring pem/cis for nausea/vomiting. Final results will be presented. Methodologies such as mixed treatment comparisons may be a useful tool for more robust comparisons of regimens than naïve comparisons with historical controls by considering a larger body of evidence and weighing factors such as sample size and quality score. However, limitations of this methodology include selection criteria for studies, publication bias, and methodological differences among studies. Although for pem/cis, efficacy differences have been associated with NSCLC histology, this methodology is limited in addressing these differences based on published data for other regimens.