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

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ABSTRACT

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). Pem/cis was non-inferior to gem/cis for survival in the overall population, but pem/cis was superior to gem/cis in patients with adenocarcinoma or large cell carcinoma and inferior in patients with squamous cell carcinoma. In addition, pem/cis demonstrated a generally more favorable toxicity profile than gem/cis. 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-seven studies, including the pem/cis versus gem/cis study, were identified; this represented 13,242 patients. Of the 27 studies, overall survival was reported in 18, one-year survival rate in 24, TtP (or PFS) in 15, and tumor response rate in 27. Thrombocytopenia was reported in 27 studies, neutropenia and anemia each in 26, nausea/vomiting in 24, febrile neutropenia in 18, and diarrhea in 13. Preliminary results with random effect modelling are reported. Hazard ratios for overall survival ranged from 0.89 to 1.16, with all 95% confidence intervals (CIs) including 1, but numerically favoring pem/cis. Hazard ratios for TtP ranged from 0.31 to 1.22, 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 naive 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.

Note: Abstract results were updated based on inclusion of one additional publication.

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)
  - Pem/cis was non-inferior to gem/cis for survival in the overall population, but pem/cis was superior to gem/cis in patients with adenocarcinoma or large cell carcinoma and inferior in patients with squamous cell carcinoma
  - In addition, pem/cis demonstrated a generally more favorable toxicity profile than gem/cis
- In absence of randomized head-to-head data of pem/cis with other commonly used first-line regimens, one must rely on indirect comparisons

Objective

- To compare pem/cis with recommended first-line platinum-based therapies for advanced NSCLC
  - Endpoints of interest: overall survival, one-year survival rate, time to progression (TtP), tumor response rate, and select grade 3/4 toxicities

METHODS

- A mixed treatment comparison (MTC) is a conservative form of indirect comparison that considers a network built from available relevant data (Lu & Ades, Stat Med 2004)
  - –Extension of standard pairwise meta-analysis
  - –Uses both direct and indirect evidence to estimate parameters
  - –Considers relative differences between regimens
- Network was built using published data for: (1) doublets of pem, docetaxel (doc), gem, paclitaxel (pac) and vinorelbine (vin) plus cis or carboplatin (cb); and (2) platinum triplets with bevacizumab (bev)

Literature Review

- English-language manuscripts published 1995 to September 2007 and abstracts from 2006 and 2007 from ASCO and IASLC
- Inclusion criteria:
  - –Randomized
  - –≥1 regimen of interest or support of network
  - –Stage IIIB and/or IV
  - –Performance status (PS) ≤2 (or Karnofsky status ≥70)
  - –No prior chemotherapy
- Exclusion criteria:
  - –Stage IIIA
  - –Studies limited to elderly or poor PS
  - –Treatment modalities other than chemotherapy

Data Extraction

- Data were extracted using a pre-specified template
- Updated results from secondary publications were used when available
- Hazard ratios for overall survival and TtP
  - Progression-free survival (PFS) was substituted when TtP was not reported
  - If hazard ratios were not reported, when possible, these were estimated from other summary data using methodology proposed by Parmar et al (Stat Med 1998)
- Rates of one-year survival, tumor response and toxicities
  - When both nausea and vomiting were reported, the higher rate of the two was used in the analysis
- Quality of studies were rated using the European Lung Cancer Working Party criteria

Analysis

- Each outcome was analyzed independently, relative to pem/cis outcomes
- Data for regimens were pooled, regardless of dosing variations
  - Exception: paclitaxel 24-hr infusion vs 3-hr infusion
- Analyses were conducted using WinBUGS software
- Analyses were conducted with fixed effect and random effect modelling
  - Random effect modelling does not assume homogeneity across the studies
- Results are reported as hazard ratios for time-to-event outcomes and odds ratios for rates
- 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

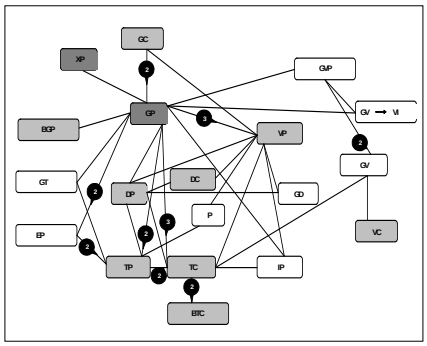
RESULTS

Summary of Analyzed Studies

	Regimens Supporting Network[1]	Overall Survival	One-year survival	TtP (or PFS)	Tumor response	Anemia	Thrombo-cytopenia	Neutropenia	Febrile Neutropenia	Nausea/ vomiting	Diarrhea
Scagliotti et al, Proc WCLC 2007[1]	Pem/cis (n=862) Gem/cis (n=863)	X	X	X	X	X	X	X	X	X	X
Alberola et al, J Clin Oncol 2003	Gem/cis (n=182) *Gem/vin/cis (n=188)* *Gem/vin → vin/ifos (n=187)*		X		X	X	X	X	X	X	
Belani et al, Ann Oncol 2005	Pac/cb 3 (n=190) *Etop/cis (n=179)*		X		X	X	X	X		X	
Bonomi et al, J Clin Oncol 2000	Pac/cb 24 (n=381) *Etop/cis (n=193)*		X		X	X	X[3]	X[3]		X[3]	
Cardenal et al, J Clin Oncol 1999	Gem/cis (n=69) *Etop/cis (n=64)*	X	X	X	X	X	X	X	X	X	
Esteban et al, Invest New Drugs 2006	*Gem/vin (n=57)* *Gem/vin/cis (n=57)*		X		X	X	X	X	X	X	
Fossella et al, J Clin Oncol 2003	Doc/cis (n=408) Doc/cb (n=406) Vin/cis (n=404)	X	X		X	X	X	X	X	X	X
Gatzemeier et al, J Clin Oncol 2000	Pac/cis 3 (n=207) *Cis (n=207)*	X	X	X	X	X	X	X	X	X	
Gebbia et al, Lung Cancer 2003	Gem/cis (n=138) Vin/cis (n=140)		X		X	X	X	X		X	
Johnson et al, J Clin Oncol 2004	Pac/cb 3 (n=32) Pac/cb/bev 7.5 (n=32) Pac/cb/bev 15 (n=34)			X	X		X			X	X
Katakami et al, J Thorac Oncol 2006	Doc/cis (n=68) *Doc/gem (n=63)*	X	X		X	X	X	X	X	X	X
Kelly et al, J Clin Oncol 2001	Pac/cb (n=206) Vin/cis (n=202)	X	X		X	X	X	X		X	
Laack et al, J Clin Oncol 2004	*Gem/vin (n=143)* *Gem/vin/cis (n=144)*	X	X	X	X	X	X	X		X	X
Lilenbaum et al, Ann Oncol 2005	Pac/cb 3 (n=83) *Gem/vin (n=82)*		X		X	X	X	X	X		
Manegold et al, Proc ASCO 2007	Gem/cis (n=347) Gem/cis/bev 7.5 (n=345) Gem/cis 15 (n=351)			X	X	X	X	X	X	X	
Mazzanati et al, Lung Cancer 2003	Gem/cis (n=62) Gem/cb (n=58)	X	X	X	X	X	X	X		X	X
Ohe et al, Ann Oncol 2007	Gem/cis (n=146) Pac/cb 3 (n=145) Vin/cis (n=145) *Irin/cis (n=145)*	X	X		X	X	X	X	X	X	X
Pujol et al, Ann Oncol 2005	Vin/cis (n=156) *Gem/doc (n=155)*	X	X	X	X	X	X	X	X		
Rosell et al, Ann Oncol 2002	Pac/cis 3 (n=309) Pac/cb 3 (n=309)	X	X	X	X	X	X	X	X	X	X
Sandler et al, NEJM 2006	Pac/cb (n=433) Pac/cb/bev (n=417)	X	X	X	X	X[3]	X[3]	X[3]	X		
Scagliotti et al, J Clin Oncol 2002	Gem/cis (n=205) Pac/cb (n=201) Vin/cis (n=201)	X	X	X	X	X	X	X	X	X	
Schiller et al, NEJM 2002	Doc/cis (n=289) Gem/cis (n=288) Pac/cis 24 (n=288) Pac/cb (n=290)	X	X	X	X	X	X	X	X	X	X
Smit et al, J Clin Oncol 2003	Gem/cis (n=160) Pac/cis 3 (n=159) *Gem/pac (n=161)*	X	X	X	X	X	X	X	X	X	
Tan et al, Lung Cancer 2005	Vin/cb (n=159) *Gem/vin (n=157)*	X	X		x	X	X	X	X	X	X
Thomas et al, Lung Cancer 2006	Gem/cb (n=51) Vin/cis (n=48)				X	X	X	X	X	X	X
Wozniak et al, J Clin Oncol 1998	Vin/cis (n=206) *Cis (n=209)*	X	X	X	X	X	X	X		X	X
Zatloukal et al, Lung Cancer 2003	Gem/cis (n=87) Gem/cb (n=89)	X	X	X	X	X	X	X		X	X
TOTAL	**27 studies (13,242 patients)**	**18**	**24**	**15**	**27**	**26**	**27**	**26**	**18**	**24**	**13**

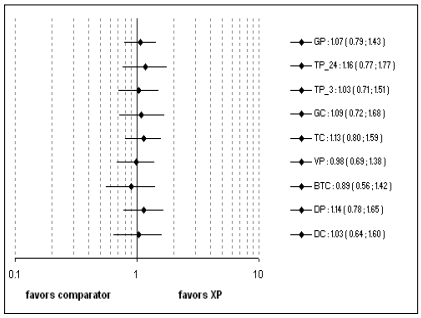
[1] Non-target regimens are italicized; [2] detailed results in Scagliotti et al, J Clin Oncol 2008; [3] only grade 4 reported

Mixed Treatment Comparison Network



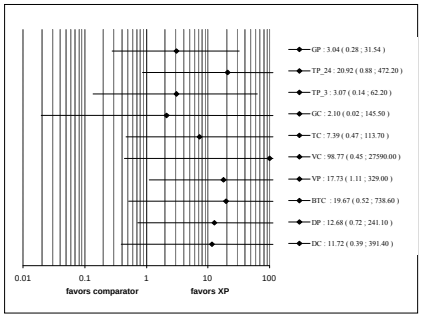
XP: pem/cis; GC: gem/cb; GVP: gem/vin/cis; BGP: gem/cis/bev; GP: gem/cis; VP: vin/cis; GV→VI: gem/vin → vin/ifosfamide; GT: gem/pac; DP: doc/cis; DC: doc/cb; P: cis; GD: gem/doc; GV: gem/vin; EP: etoposide/cis; VC: vin/cb; TP: pac/cis: TC: pac/cb; IP: ifosfamide/cis; BTC: pac/cb/bev

Overall Survival



XP: pem/cis; GP: gem/cis; TP_24: pac/cis 24-hr infusion;TP_3: pac/cis 3-hr infusion; GC: gem/cb; TC: pac/cb; VC: vin/cb; VP: vin/cis; BTC: pac/cb/bev; DP: doc/cis; DC: doc/cb

Febrile Neutropenia



XP: pem/cis; GP: gem/cis; TP_24: pac/cis 24-hr infusion;TP_3: pac/cis 3-hr infusion; GC: gem/cb; TC: pac/cb; VC: vin/cb; VP: vin/cis; BTC: pac/cb/bev; DP: doc/cis; DC: doc/cb

- Results for other endpoints:
  - Odds ratios for one-year survival and tumor response rates included 1
  - Odds ratios for toxicities included 1
    - Numerical trends favoring pem/cis for neutropenia, but not favoring for nausea/vomiting
- Sensitivity analyses had little impact on results

CONCLUSIONS

- 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
- Methodologies such as mixed treatment comparisons may be a useful tool for more robust comparisons of regimens by considering a larger body of evidence and weighing factors such as sample size and quality score
  - Limitations of this methodology include selection criteria for studies, publication bias, and methodological differences among studies.
  - Efficacy differences by NSCLC histology could not be addressed by this methodology due to lack of published data for most regimens

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