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Survival without toxicity for cisplatin plus pemetrexed versus cisplatin plus gemcitabine in chemonaïve patients with advanced non-small cell lung cancer: A risk-benefit analysis of a large phase III study

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ABSTRACT

Background: In a large phase III study, cisplatin and pemetrexed had non-inferior efficacy and better tolerability compared with cisplatin and gemcitabine in chemonaïve patients with non-small cell lung cancer (NSCLC). The current analysis characterised the clinical benefit (i.e. survival) relative to clinical risk (i.e. drug-related toxicity) of the doublets.

Patients and methods: A total of 1669 patients (of 1725 randomised) received 500 mg/m^2 pemetrexed IV followed by 75 mg/m^2 cisplatin IV on day 1 or gemcitabine 1250 mg/m^2 on days 1 and 8 and 75 mg/m^2 cisplatin on day 1, administered every 3 weeks for up to 6 cycles. Survival without toxicity (i.e. clinical benefit to risk) was defined as the time from randomisation to the first occurrence of any grade 3 or 4 drug-related toxicity or death, and was analysed using Kaplan–Meier and Cox methods.

Results: In the overall patient population, survival without grade 3 or 4 drug-related toxicity was significantly longer for patients treated with cisplatin and pemetrexed versus cisplatin and gemcitabine (HR = 0.70; $P < 0.001$), as was survival without grade 4 drug-related toxicity (HR = 0.83; $P < 0.001$). For patients with non-squamous NSCLC, survival without toxicity with cisplatin and pemetrexed was superior to cisplatin and gemcitabine for grade 3 or 4 drug-related toxicity (HR = 0.64; $P < 0.001$) and for grade 4 drug-related toxicity (HR = 0.77; $P < 0.001$), whereas no treatment-arm difference was observed in the squamous subgroup.

Conclusions: Patients with non-squamous NSCLC treated with front-line cisplatin and pemetrexed have superior survival without toxicity (i.e. clinical benefit-to-risk profile) compared with patients treated with cisplatin and gemcitabine.

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1. Introduction

The majority of patients with newly diagnosed non-small cell lung cancer (NSCLC) present with inoperable disease,[1] and platinum-based doublets are recommended as front-line treatment for these patients.[2,3] Cytotoxic agents clinically tested in combination with cisplatin or carboplatin include pemetrexed, gemcitabine, vinorelbine, irinotecan and taxanes.[4–13] When evaluated head-to-head in phase III studies, these platinum-based doublets have demonstrated comparable efficacy with diverse toxicity profiles.[10–13] Thus, the toxicity profile of a regimen may be a relevant variable that affects the choice of front-line treatment.

The favourable toxicity profile of pemetrexed and its efficacy in thoracic tumours, both in combination with cisplatin for mesothelioma[14] and as a single agent in the second-line treatment of NSCLC,[15] led to a large phase III study of cisplatin and pemetrexed versus cisplatin and gemcitabine in chemonaïve patients with stage IIIB/IV advanced NSCLC.[16] This study demonstrated non-inferior efficacy and better tolerability for cisplatin and pemetrexed. In a pre-specified analysis of histology,[17] a significantly longer survival time was observed in the non-squamous subgroup treated with cisplatin and pemetrexed versus cisplatin and gemcitabine (median survival 11.1 versus 10.1 months; hazard ratio [HR] = 0.84 [95% CI: 0.74–0.96]; $P = 0.011$). In the squamous subgroup, a shorter survival time was observed in patients treated with cisplatin and pemetrexed (median survival 9.4 versus 10.8 months; HR = 1.23 [95% CI: 1.00–1.51]; $P = 0.050$).[17]

Although cytotoxic chemotherapy improves survival in advanced NSCLC, its impact may be hampered by clinically relevant toxicities. Pujol et al.[18] reported a novel method of quantifying a clinical benefit-to-risk profile based on each patient's time from randomisation to the first occurrence of grade 3 or 4 toxicity or death due to any cause. This duration provides a measure of the clinical benefit of a treatment (i.e. overall survival time) relative to the clinical risk (i.e. the first occurrence of grade 3 or 4 toxicity or death). In the current analysis, we applied the method of Pujol et al.[18] to compare the clinical benefit relative to the clinical risk of cisplatin and pemetrexed versus cisplatin and gemcitabine.[16]

2. Patients and methods

2.1. Patients

Data for this analysis were extracted from the database of the phase III study[16] that included chemonaïve patients at least 18 years of age with histologically or cytologically confirmed NSCLC classified as stage IIIB not amenable to curative treatment or stage IV. Patients had at least one unidimensionally measurable lesion according to Response Evaluation Criteria in Solid Tumours (RECIST),[19] an Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 and adequate bone marrow reserve and organ function. Patients were excluded from the study for National Cancer Institute Common Toxicity Criteria[20] (NCI-CTC; version 2.0) grade $\geqslant 1$ peripheral neuropathy, progressive brain metastases or uncontrolled third-space fluid retention. The protocol was conducted according to the Declaration of Helsinki and Good Clinical Practice guidelines[21] and was approved by each participating institution's ethics review board. All patients signed written informed consent before treatment.

2.2. Treatment and study design

Patients were randomised to receive either pemetrexed (500 mg/m^2 IV) followed by cisplatin (75 mg/m^2 IV) on day 1 or gemcitabine 1250 mg/m^2 on days 1 and 8 with cisplatin (75 mg/m^2 IV) on day 1. Both regimens were administered every 3 weeks, for a maximum of 6 cycles. Patients were randomly assigned according to disease stage (IIIB versus IV), performance status (0 versus 1), history of brain metastases (yes versus no), sex (male versus female), basis for initial pathologic diagnosis (histologic versus cytologic) and investigative centre. All patients received dexamethasone prophylaxis and folic acid and vitamin B_{12} supplementation.

2.3. Analysis of survival without toxicity

The duration of survival without toxicity was defined as the time from randomisation to the first occurrence of CTC grade 3 or 4 drug-related toxicity or death due to any cause. Survival without toxicity durations were censored at the date of the last contact for patients who were still alive and who did not have any grade 3 or 4 drug-related toxicity. Durations for all randomised patients who received at least one dose of pemetrexed, gemcitabine or cisplatin were analysed using the Kaplan–Meier method[22]; treatment-arm comparisons were based on a Cox[23] estimate for the survival without toxicity HR. The analysis was also performed separately in patients grouped by non-squamous or squamous histology. The non-squamous histology subgroup was defined as adenocarcinoma, large cell carcinoma and 'other' histology.[17] 'Other' histology comprised histologic diagnoses that did not clearly qualify as adenocarcinoma, large cell carcinoma or predominantly squamous cell carcinoma.

To test the statistical robustness of the results, the analysis was repeated using two alternative definitions of clinical risk that considered: (i) only grade 4 drug-related toxicities or death, and (ii) a selection of the most clinically relevant, grade 3 or 4 drug-related toxicities or death as previously defined.[18]

3. Results

Between July 2004 and December 2005, a total of 1725 patients with advanced NSCLC were randomly assigned to cisplatin and pemetrexed or cisplatin and gemcitabine. Of these patients, 1669 received treatment; 839 (235 with squamous and 604 with non-squamous histology) received cisplatin and pemetrexed and 830 (221 with squamous and 609 with non-squamous histology) received cisplatin and gemcitabine.[16] Baseline patient and disease characteristics were well balanced across treatment arms, with no statistically significant differences between arms (Table 1).

Table 1 – Patient and disease characteristics for randomised patients.

Characteristic	Cisplatin and pemetrexed (*N* = 862)	Cisplatin and gemcitabine (*N* = 863)
Age, years		
Median (range)	61.1 (28.8–83.2)	61.0 (26.4–79.4)
<65	541 (62.8%)	577 (66.9%)
Male	605 (70.2%)	605 (70.1%)
Caucasian	669 (77.6%)	680 (78.8%)
Never-smoker	128 (14.8%)	122 (14.1%)
Disease stage		
Stage IIIB	205 (23.8%)	210 (24.3%)
Stage IV	657 (76.2%)	653 (75.7%)
ECOG performance status 1	556 (64.5%)	554 (64.2%)
Histology		
Non-squamous	618 (71.7%)	634 (73.5%)
Adenocarcinoma	436 (50.6%)	411 (47.6%)
Large cell carcinoma	76 (8.8%)	77 (8.9%)
Other histologies (NSCLC and NOS)	106 (12.3%)	146 (16.9%)
Squamous cell carcinoma	244 (28.3%)	229 (26.5%)

ECOG, Eastern Cooperative Oncology Group; NOS, not otherwise specified.

In the overall study population, the tolerability of pemetrexed and cisplatin was favourable compared with that of cisplatin and gemcitabine as demonstrated by the lower rates of haematologic grade 3 or 4 drug-related toxicities (neutropaenia, 15% versus 27% of patients; anaemia, 6% versus 10% and thrombocytopaenia, 4% versus 13%; $P \leqslant 0.001$), fewer blood transfusions (16.4% versus 28.9%; $P < 0.001$) and less use of erythropoietic-enhancing agents (10.4% versus 18.1%; $P < 0.001$) and granulocyte (or granulocyte-macrophage) stimulating growth factors (3.1% versus 6.1%; $P = 0.004$).[16]

3.1. *Survival without toxicity overall analysis*

Overall survival time without grade 3 or 4 drug-related toxicity was significantly longer for patients treated with cisplatin and pemetrexed (HR = 0.70 [95% CI: 0.63–0.78]; $P < 0.001$) (Fig. 1). Median survival time without grade 3 or 4 drug-related toxicity was 5.6 months for cisplatin and pemetrexed versus 2.8 months for cisplatin and gemcitabine. The rate of survival without grade 3 or 4 drug-related toxicity at 6 months was 48.1% for cisplatin and pemetrexed and 33.3% for cisplatin and gemcitabine; the corresponding rates at 12 months were 28.6% and 17.9%, respectively.

Overall survival time without grade 4 drug-related toxicity was significantly longer for patients treated with cisplatin and pemetrexed compared with those treated with cisplatin and gemcitabine (HR = 0.83 [95% CI: 0.74–0.93]; $P < 0.001$). Median survival time without grade 4 drug-related toxicity was 9.8 months for cisplatin and pemetrexed and 8.6 months for cisplatin and gemcitabine.

When the overall analysis of survival without toxicity was done for select, clinically relevant grade 3 or 4 drug-related toxicities, a significantly longer overall survival time was observed for the cisplatin and pemetrexed arm compared with the cisplatin and gemcitabine arm (median survival time 6.3 months for pemetrexed and cisplatin versus 3.3 months for gemcitabine and cisplatin; HR = 0.71 [95% CI: 0.64–0.79]; $P < 0.001$).

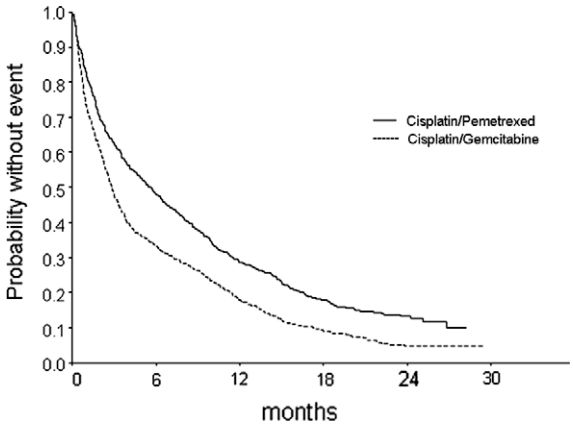

Fig. 1 – Survival without grade 3 or 4 drug-related toxicity in the overall patient population for patients treated with cisplatin and pemetrexed (*n* = 839) versus cisplatin and gemcitabine (*n* = 830).

3.2. *Survival without toxicity analysis by histology*

Patients with non-squamous histology had significantly longer overall survival time without grade 3 or 4 drug-related toxicity when treated with cisplatin and pemetrexed (HR = 0.64 [95% CI: 0.56–0.72]; $P < 0.001$) (Fig. 2). Median survival time without grade 3 or 4 drug-related toxicity was 5.9 and 2.8 months, respectively. No significant difference between arms was detected for patients with squamous cell carcinoma (median survival time 4.1 months for pemetrexed and cisplatin versus 2.9 months for cisplatin and gemcitabine; HR = 0.89 [95% CI: 0.73–1.09]; $P = 0.257$) (Fig. 3).

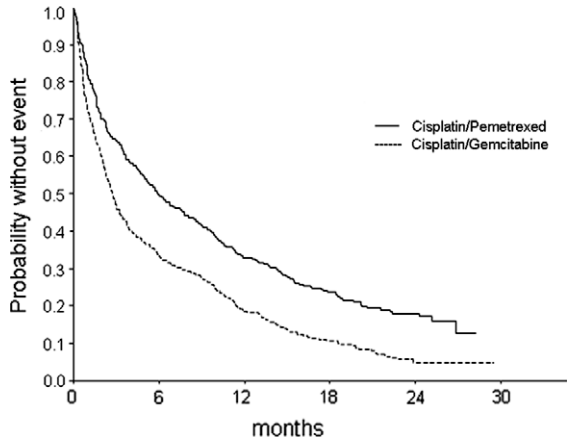

Fig. 2 – Survival without grade 3 or 4 drug-related toxicity for patients with non-squamous histology treated with cisplatin and pemetrexed (*n* = 604) versus cisplatin and gemcitabine (*n* = 609).

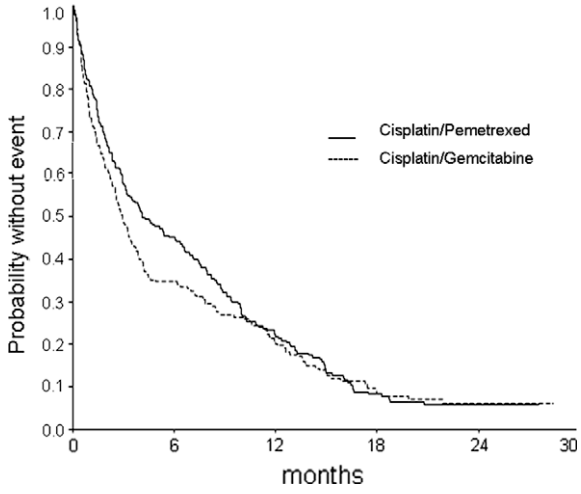

Fig. 3 – Survival without grade 3 or 4 drug-related toxicity for patients with squamous histology treated with cisplatin and pemetrexed (*n* = 235) versus cisplatin and gemcitabine (*n* = 221).

Similarly, when the analysis was repeated for grade 4 drug-related toxicity, patients with non-squamous histology had significantly longer survival when treated with cisplatin and pemetrexed (median survival time 10.2 versus 8.7 months; HR = 0.77 [95% CI: 0.68–0.88]; $P < 0.001$). No significant treatment-group difference in survival time without grade 4 drug-related toxicity was detected for patients with squamous histology (median survival time 8.7 months for pemetrexed and cisplatin versus 7.9 months for cisplatin and gemcitabine; HR = 0.99 [95% CI: 0.81–1.21]; $P = 0.906$).

4. Discussion

The current analysis evaluated the clinical benefit relative to the clinical risk of the combination of cisplatin and pemetrexed compared with cisplatin and gemcitabine based on data from a previously published phase III study.[16] The method applied to the analysis[18] was based on each patient's time from randomisation to the first occurrence of grade 3 or 4 drug-related toxicity or death due to any cause. This duration provides a measure of patient survival free from the risks associated with grade 3 or 4 drug-related toxicity. Statistical analysis of the duration of survival without toxicity can therefore provide a quantitative summary of the benefit-to-risk profile for each regimen.

Previously, Pujol et al. reported superior survival without toxicity for single-agent pemetrexed compared with that for docetaxel as second-line therapy in patients with advanced NSCLC (HR = 0.60 [95% CI: 0.50–0.72]; $P < 0.001$).[18] Our current analysis also demonstrated a superior survival without toxicity (grade 3 or 4 drug-related events) in the overall population for chemonaïve patients treated with cisplatin and pemetrexed compared with those treated with cisplatin and gemcitabine (HR = 0.70 [95% CI: 0.63–0.78]; $P < 0.001$). Consistent results were also reported for survival without grade 4 drug-related toxicity and for survival without select, clinically relevant grade 3 or 4 drug-related toxicity, thus illustrating the consistency of the clinical benefit.

Unfortunately, survival without toxicity analyses are not available for the large, randomised, clinical studies conducted in the 1990s in advanced NSCLC. However, vinorelbine doublets, for example, have been consistently associated with higher rates than comparators of grades 3 and 4 toxicities (including neutropaenia, anaemia, nausea and vomiting), hospitalisations and study discontinuations due to adverse events.[8,10,11] Likewise, irinotecan doublets have been associated with considerable toxicity, particularly myelosuppression (neutropaenia, thrombocytopaenia and leukopaenia) and high rates of grade 2 or worse nausea, vomiting and anorexia (>50% of patients, respectively).[13] Paclitaxel doublets are also more likely than comparators to produce peripheral neuropathy, arthralgia and myalgia,[8,12] and, in one study, a docetaxel regimen was associated with a considerably high incidence (>70% of patients) of grades 3 and 4 neutropaenia.[10]

In addition to the clinical benefit shown in the overall population of the current study, patients with non-squamous histology demonstrated a superior survival without grade 3 or 4 drug-related toxicity when treated with cisplatin and pemetrexed compared with cisplatin and gemcitabine (HR = 0.64 [95% CI: 0.56–0.72]; $P < 0.001$). No statistically significant treatment-arm difference in survival without grade 3 or 4 drug-related toxicity was observed in patients with squamous cell carcinoma. These results in patients with non-squamous histology are consistent with the recent observations of the pemetrexed treatment effect on survival based on histology.[16,17]

When evaluated within histologic subgroups, the toxicity profiles of cisplatin and pemetrexed and cisplatin and gemcitabine were similar to those observed in the overall study population, and both regimens were well tolerated.[17] Moreover, measures of medical resource utilisation (i.e. transfusions and the use of concomitant medications) were consistently lower with cisplatin and pemetrexed across histology subgroups, just as they were in the overall study population.[24] Given these observations, it is possible that the significant differences observed with these analyses for survival without toxicity are related to the histologically based pemetrexed

treatment effect on survival, rather than to the safety advantage of cisplatin and pemetrexed over cisplatin and gemcitabine.

The results of the current survival without toxicity analysis in the overall study population confirm the superior benefit-to-risk profile of pemetrexed previously reported.[18] In addition, the survival without toxicity results in patients with non-squamous histology reflect superior survival and the pemetrexed treatment effect previously reported by Scagliotti et al. whereas the results in patients with squamous cell carcinoma reflect shorter survival times as previously reported.[16,17]

The combination of the safety and survival benefit observed with cisplatin and pemetrexed in this survival without grade 3 or 4 drug-related toxicity analysis suggests a superior clinical benefit-to-risk advantage for this combination compared with the cisplatin and gemcitabine combination in patients with non-squamous NSCLC.

Conflict of interest statement

Dr. Renato Martins received honoraria and research funding from Eli Lilly and Company. Dr. Keunchil Park received an honorarium from Eli Lilly and Company for an Advisory meeting. Drs. Carla Visseren-Grul and Patrick Peterson are employees of Eli Lilly and Company, and as such, own Lilly stock. Dr. Tuncay Goksel received honoraria from Sanofi-Aventis, AstraZeneca, Roche and GlaxoSmithKline. Dr. Giorgio Scagliotti received honoraria from Eli Lilly and Company, Sanofi-Aventis, Roche, GlaxoSmithKline, AstraZeneca and Boehringer Ingelheim. Drs. Steven J.M. Gans, Shekar Patil and Janusz Rolski have no relationships to disclose.

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