Lung Cancer: Targets and Therapy

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ORIGINAL RESEARCH

# Combination chemotherapy of gemcitabine and vinorelbine for pretreated non-small-cell lung cancer: a retrospective study



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**Background:** Advanced non-small-cell lung cancer (NSCLC) eventually progresses after first-line chemotherapy, and usually requires salvage treatment. Although neither gemcitabine nor vinorelbine is approved as a candidate drug in the second- or further-line for NSCLC, they can be alternative drugs in terms of anti-tumor effects and toxicities. Actually, in our institution, we often use a combination of these two anti-tumor drugs in our daily practice.

**Methods:** We retrospectively reviewed 85 patients with advanced NSCLC who had received combination chemotherapy of gemcitabine and vinorelbine after a platinum-based regimen from June 2007 to June 2014 in Osaka Police Hospital, and performed Cox proportional hazard analyses in order to detect predictive factors for progression-free survival (PFS).

**Results:** Patient characteristics included a mean age of 65.5 years, 56 males, 54 adenocarcinoma, 53 European Clinical Oncology Group performance status 0–1. Thirteen and 35 patients received the study treatment as the second- and third-line treatment, respectively. The overall response rate, disease control rate, PFS, and overall survival were 4.7% (95% confidence interval 1.3%–11.6%), 30.6% (21.0%–41.5%), 2.1 months (1.7–2.8 months), and 6.9 months (5.0–11.0 months). Twenty-one and six patients experienced grade 4 neutropenia and febrile neutropenia, respectively. European Clinical Oncology Group performance status 0–1 was detected as a factor predicting longer PFS by univariate (hazard ratio, 1.63; 95% confidence interval, 1.28–2.08; $P<0.001$) and multivariate (1.65, 1.27–2.14, $P<0.001$) analyses.

**Conclusion:** This combination was ineffective and harmful to pretreated patients with NSCLC. We do not recommend this regimen as a later-line treatment option.

**Keywords:** gemcitabine, vinorelbine, non-small cell lung cancer, performance status, retrospective study, combination chemotherapy

## Introduction

The majority of non-small-cell lung cancer (NSCLC) is already inoperable at the time of diagnosis and requires systemic chemotherapy. However, almost all patients with advanced NSCLC eventually experience disease progression even after standard platinum-based chemotherapy. Only 69%, 38%, and 18% of patients received the second-, third-, and fourth-line chemotherapy in a Japanese cancer center.[1] Currently, three anti-tumor drugs: docetaxel,[2] pemetrexed,[3] and erlotinib,[4] have been pivotal options for second-line regimens. Unfortunately, monotherapy using any of these agents has provided only around 10% response. Moreover, no regimen has been recognized as an established third- or further-line regimen.

Gemcitabine and vinorelbine are a pyrimidine antimetabolite and a semi-synthetic vinca alkaloid drug, respectively. Owing to their cytotoxic effects and mild toxicities,

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these two drugs as monotherapy have been approved as a standard regimen for chemo-naïve elderly patients with advanced NSCLC.[5,6] On the other hand, combination of these two drugs also showed favorable efficacy and tolerability in many Phase II and III trials for untreated and pretreated NSCLC patients, around the year 2000. There were two Italian Phase III trials that focused on chemo-naïve elderly patients aged ≥70 years.[6,7] Combination of gemcitabine and vinorelbine was less effective and more toxic than the two drugs given singly in one study,[6] but successfully provided longer survival and delayed deterioration of symptoms and quality-of-life than vinorelbine monotherapy in the other study.[7,8] There were also two Phase III trials that had compared this combination regimen with platinum-based and vinorelbine-containing regimens in the first-line setting.[9,10] The combination of gemcitabine and vinorelbine failed to show significant survival advantage compared with platinum-based regimens. Based on these results, we have often used this combination regimen in our daily practice for progressive NSCLC after a platinum-based regimen.

The aim of our study was to retrospectively evaluate combination chemotherapy of gemcitabine and vinorelbine for pretreated patients with NSCLC.

**Table 1** Patient characteristics (N=85)

| | |
|---|---|
| Age, years | |
| Mean ± SD | 65.5±9.7 |
| Sex | |
| Male/female | 56/29 |
| Histology | |
| Ad/Sq/others | 54/23/8 |
| Staging | |
| III/IV/post-surgical recurrence | 20/58/7 |
| Distant metastases | |
| Brain metastasis | 25 |
| Bone metastasis | 15 |
| Liver metastasis | 13 |
| Intra-pulmonary or pleural metastasis | 38 |
| ECOG performance status | |
| 0–1/2/3 | 53/24/8 |
| EGFR mutation status | |
| Positive/wild-type/not evaluated | 9/42/34 |
| Number of prior regimens | |
| 1/2/≥3 | 13/35/37 |
| Median (range) | 2 (1–6) |
| Prior anti-tumor drugs | |
| Carboplatin | 82[a] |
| Cisplatin | 5[a] |
| Docetaxel | 38 |
| EGFR-TKI | 38 |
| Pemetrexed | 26 |

**Note:** [a]Two patients previously received both carboplatin- and cisplatin-containing regimens.

**Abbreviations:** Ad, adenocarcinoma; ECOG, European Clinical Oncology Group; SD, standard deviation; Sq, squamous cell carcinoma; TKI, tyrosine-kinase inhibitor.

**Table 2** Treatment (N=85)

| | |
|---|---|
| Number of delivered courses | |
| 1/2/3/4/≥5 | 20/20/12/16/17 |
| Mean ± SD | 3.1±1.9 |
| Discontinuation reasons (N) | |
| Progressive disease | 56 |
| Deteriorated conditions | 13 |
| Completion of 4–8 courses | 9 |
| Complicated diseases | 3 |
| Adverse effects | 3 |
| Lost to follow-up | 1 |
| Initial dose intensity (%), mean ± SD | |
| Gemcitabine (1,000 mg/m$^2$) | 80.9±14.0 |
| Vinorelbine (25 mg/m$^2$) | 80.7±15.2 |
| Total dose intensity (%), mean ± SD | |
| Gemcitabine | 66.8±16.8 |
| Vinorelbine | 67.3±18.0 |

**Abbreviation:** SD, standard deviation.

# Methods

## Patient selection and experimental design

The study was carried out at the Osaka Police Hospital. We retrospectively reviewed the medical records and collected data on patients who met all of the following criteria: 1) histologically or cytologically confirmed NSCLC; 2) stage III/IV or post-surgical recurrence; 3) disease progression after first or further-line chemotherapy, including platinum-based regimen; 4) patients who had received combination chemotherapy of gemcitabine and vinorelbine from June 2007 to June 2014 at our institution. The data collected from all of the patient medical records included the following: sex; age; histological type; European Clinical Oncology Group (ECOG) performance status (PS); distant metastases; EGFR mutation status; prior and post-treatment regimens; progression-free survival (PFS), and overall survival (OS) from the start of the combination regimen; efficacy; treatment schedule and adverse effects. The Osaka Police Hospital ethics committee approved this study and waived the requirement for informed consent (approval number 106).

**Table 3** Post-protocol chemotherapy

| | |
|---|---|
| Number of regimens | |
| 0/1/2/≥3 | 32/27/14/12 |
| Median (range) | 1 (0–10) |
| Anti-tumor drugs | |
| EGFR-TKI | 25 |
| S-1 | 21 |
| Docetaxel | 13 |
| CPT-11 | 13 |
| Pemetrexed | 7 |
| Gemcitabine | 4 |

**Abbreviations:** CPT-11, irinotecan; S-1, oral 5-fluorouracil derivative consisting tegafur, gimeracil and oteracil potassium; TKI, tyrosine-kinase inhibitor.

**Table 4** Efficacy (N=85)

| Efficacy | All (N=85) | Third- or further-line (N=72) |
|---|---|---|
| Complete response (N) | 0 | 0 |
| Partial response (N) | 4 | 4 |
| Stable disease (N) | 22 | 20 |
| Progressive disease (N) | 48 | 41 |
| Not evaluated (N) | 11 | 7 |
| Overall response rate (95% CI) (%) | 4.7 (1.3–11.6) | 5.6 (1.5–13.6) |
| Disease control rate (95% CI) (%) | 30.6 (21.0–41.5) | 33.3 (22.7–45.4) |

**Abbreviation:** CI, confidence interval.

## Treatment plan

As a rule, gemcitabine (1,000 mg/m$^2$, day 1 and 8) and vinorelbine (25 mg/m$^2$, day 1 and 8) were administered intravenously every 3 weeks. Although chemotherapeutic course was not defined, treatment was discontinued at the time of disease progression, unacceptable toxicity, or withdrawal of consent.

## Assessments

Required baseline assessments included, at least, chest and abdominal computed tomography (CT) within 1 month before treatment. Response was evaluated according to RECIST version 1.1.[11] Toxicity was graded by the National Cancer Institute-Common Terminology Criteria for Adverse Events version 4.0.[12]

The evaluable population for overall response included all patients, defined as those who had received at least one cycle chemotherapy and had at least two response assessments over 6 weeks after the introduction unless objective progressive disease was determined. Patients who received the study therapy were considered evaluable for PFS, OS, and safety. PFS and OS were evaluated by Kaplan–Meier method.

## Data analysis

The data for normally distributed continuous variables, discrete variables, and categorical variables were expressed

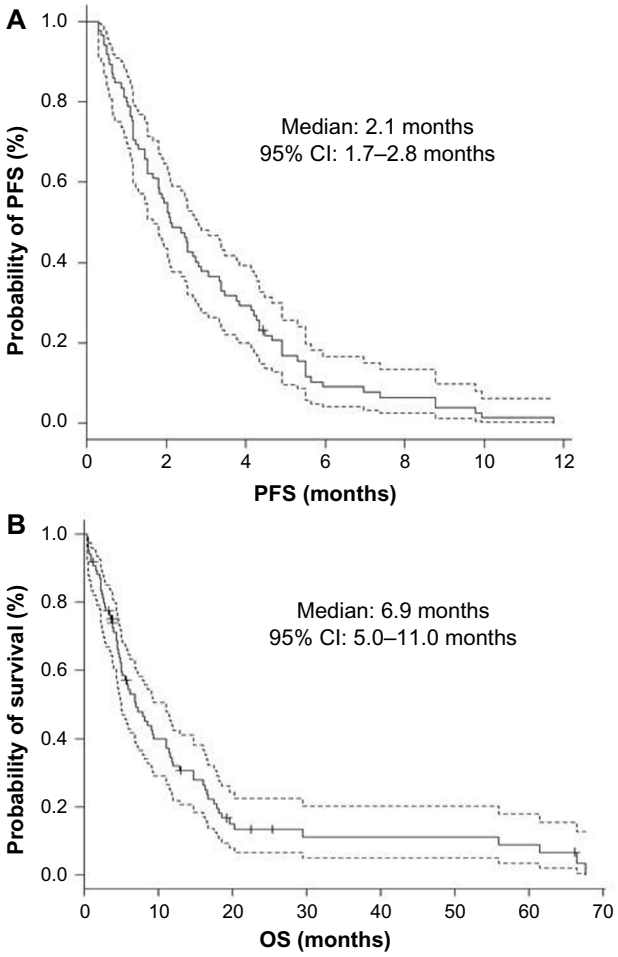


**Figure 1** Kaplan–Meier curves (solid line) of all participants (N=85).
**Notes:** (**A**) Progression-free survival (PFS); and (**B**) overall survival (OS) of gemcitabine and vinorelbine treatment with 95% confidence band (dashed lines).
**Abbreviation:** CI, confidence interval.

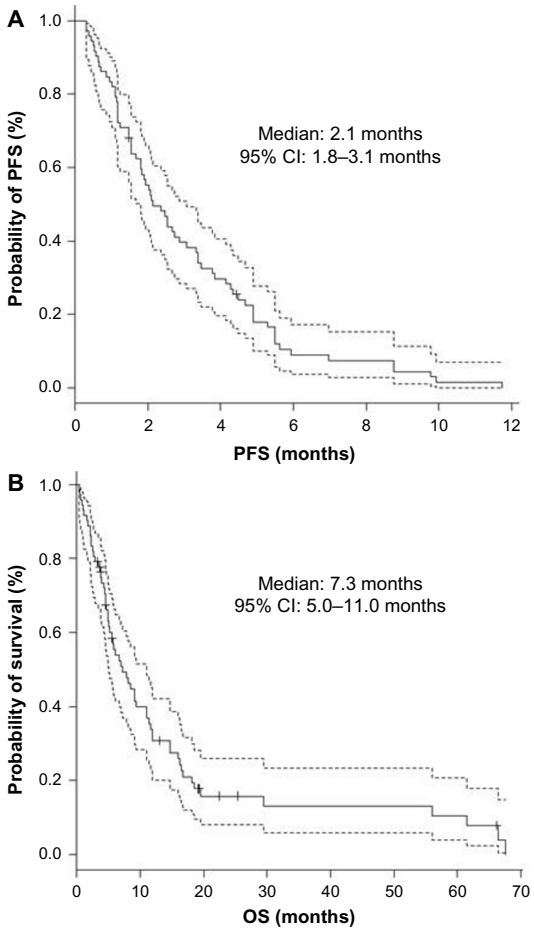


**Figure 2** Kaplan–Meier curves (solid line) of third- and further-line chemotherapy (N=72).
**Notes:** (**A**) Progression-free survival (PFS); and (**B**) overall survival (OS) of gemcitabine and vinorelbine treatment with 95% confidence band (dashed lines).
**Abbreviation:** CI, confidence interval.

**Table 5** Adverse effects (N=85)

| | Grade | | | |
|---|---|---|---|---|
| | 1 | 2 | 3 | 4 |
| Hematological (N) | | | | |
| Leukopenia | 13 | 20 | 23 | 8 |
| Neutropenia | 11 | 4 | 25 | 21 |
| Hemoglobin decrease | 22 | 41 | 17 | 0 |
| Thrombocytopenia | 21 | 24 | 11 | 0 |
| Non-hematological (N) | | | | |
| Aminotransferase increase | 40 | 5 | 2 | 0 |
| Serum creatinine increase | 6 | 0 | 0 | 0 |
| Febrile neutropenia | 0 | 0 | 6 | 0 |
| Anorexia | 38 | 13 | 11 | 0 |
| Nausea or vomiting | 16 | 7 | 0 | 0 |
| Fatigue | 20 | 11 | 1 | 0 |
| Constipation | 21 | 23 | 4 | 0 |
| Diarrhea | 12 | 1 | 0 | 0 |
| Oral mucositis | 6 | 4 | 0 | 0 |
| Vasculitis | 4 | 5 | 0 | 0 |
| Rash | 10 | 6 | 0 | 0 |
| Fever | 18 | 2 | 0 | 0 |

as the mean ± standard deviation, median (range), and frequency. To examine how patients' backgrounds influenced survival, the following seven background variables were added as an independent variable in the Cox proportional hazard regression model: ECOG PS, sex, age, histology, prior regimens, distant metastases, and initial dose reduction rate of gemcitabine. We excluded the initial dose reduction rate of vinorelbine as an independent variable because dose reductions of these two anti-tumor drugs were closely correlated. The results were evaluated in terms of the hazard ratio (HR) and 95% confidence interval (CI). A $P$-value $<0.05$ was considered as being statistically significant.

All statistical analyses were performed with EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics.[13]

## Results

During the study period, 88 patients received combination chemotherapy. Two patients received the study regimen as first-line chemotherapy. One patient had been treated only with EGFR-tyrosine-kinase inhibitors prior to the study regimen. Thus, these three patients were excluded from the analyses. As of March 31, 2015, all patients discontinued the study regimen, three were still alive and nine lost to follow-up. Patient baseline characteristics are shown in Table 1. Eight patients had ECOG PS of 3, and 37 patients received the study regimen in the fourth- or further-line setting. The study treatment administered is presented in Table 2. The initial doses of gemcitabine and vinorelbine were reduced by physicians to less than 800 and 20 mg/m$^2$ in 49 and 46 patients, respectively. Forty-two, 18, and 38 patients required dose reduction after the second course, delay of the next course, and skipped administration of day 8, respectively. Table 3 describes post-protocol chemotherapy. The study regimen was the last chemotherapy in 32 patients.

**Table 6** Univariate and multivariate Cox proportional hazard analysis of factors influencing progression-free survival (N=85)

| Risk factors | Univariate | | | Multivariate | | |
|---|---|---|---|---|---|---|
| | HR | 95% CI | P | HR | 95% CI | P |
| Age | | | | | | |
| ≥70 years vs <70 years | 0.76 | 0.47–1.21 | 0.24 | 0.70 | 0.43–1.13 | 0.15 |
| Sex | | | | | | |
| Male vs female | 1.19 | 0.75–1.89 | 0.47 | 0.90 | 0.52–1.54 | 0.69 |
| ECOG PS | | | | | | |
| 2–3 vs 0–1 | 1.63 | 1.28–2.08 | <0.001 | 1.65 | 1.27–2.14 | <0.001 |
| Histology | | | | | | |
| Adenocarcinoma vs others | 0.66 | 0.42–1.04 | 0.07 | 0.74 | 0.42–1.30 | 0.29 |
| Distant metastases | | | | | | |
| Yes vs no or not evaluated | 1.07 | 0.66–1.73 | 0.80 | 1.34 | 0.76–2.38 | 0.31 |
| Number of prior regimens | | | | | | |
| ≥3 vs 1–2 | 0.74 | 0.48–1.16 | 0.19 | 0.76 | 0.46–1.27 | 0.30 |
| Gemcitabine initial dose reduction rate (%) | | | | | | |
| ≥80% vs <80% | 1.07 | 0.69–1.67 | 0.76 | 0.95 | 0.60–1.50 | 0.81 |

**Notes:** Coded as 1 (≥70 years, male, ECOG PS 2–3, adenocarcinoma histology, positive distant metastases, ≥3 prior regimens, and initial gemcitabine dose of more than 80%) and as 0 (<70 years, female, ECOG PS 0–1, non-adenocarcinoma histology, 1–2 prior regimens and initial gemcitabine dose of less than 80%).
**Abbreviations:** CI, confidence interval; ECOG PS, European Clinical Oncology Group performance status; HR, hazard ratio.

The overall response rate (RR), disease control rate, PFS, and OS of all 85 patients were 4.7% (95% CI, 1.3%–11.6%), 30.6% (21.0%–41.5%), 2.1 months (1.7–2.8 months), and 6.9 months (5.0–11.0 months), while those of 72 patients in the third- or further-line were 5.6% (1.5%–13.6%), 33.3% (22.7%–45.4%), 2.1 months (1.8–3.1 months), and 7.3 months (5.0–11.0 months), respectively (Table 4, Figures 1 and 2). All four patients who achieved partial response had received the study regimen as the third- or further-line treatment. Twenty-one and six patients suffered from grade 4 neutropenia and febrile neutropenia, respectively (Table 5). Seven patients died within a month after introduction of the study regimen. All of them initially had ECOG PS of 2 or 3, and consequently progressed or could not be evaluated owing to rapidly deteriorated symptoms. Both univariate and multivariate analyses detected ECOG PS 0–1 as a factor predicting longer PFS (univariate; HR 1.63, 95% CI 1.28–2.08, $P<0.001$, multivariate; HR 1.65, 95% CI 1.27–2.14, $P<0.001$) (Table 6).

## Discussion

This was a retrospective study in practical use of combination regimen of gemcitabine and vinorelbine for patients with advanced NSCLC previously treated with platinum-based regimen.

**Table 7** Review of prospective studies of combination chemotherapy of gemcitabine and vinorelbine for pretreated patients

| Authors (year) | N | Phase | Line | Dose and schedule | RR<br>DCR | PFS | OS |
|---|---|---|---|---|---|---|---|
| Camps et al (2000)[15] | 16 | Pilot | 2nd | G 1,200 mg/m$^2$ (Day 1, 8, 15)<br>V 25 mg/m$^2$ (Day 1, 8)<br>Every 28 days, until PD | 6.25%<br>37.5% | ND | 25 W |
| Hainsworth et al (2000)[18] | 55 | II | 2nd | G 1,000 mg/m$^2$ (Day 1, 8, 15)<br>V 20 mg/m$^2$ (Day 1, 8)<br>Every 28 days | 18%<br>66% | 5.0 M[a] | 6.5 M |
| Kosmas et al (2001)[22] | 40 | II | 2nd | G 1,000 mg/m$^2$ (Day 1, 8)<br>V 25 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 22.5%<br>55% | 4.5 M | 7 M |
| Pectasides et al (2001)[24] | 39 | II | 2nd | G 800 mg/m$^2$ (Day 1, 8)<br>V 25 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 2.6%<br>64.1% | 4.7 M | 7.3 M |
| Herbst et al (2002)[20] | 36 | II | 2nd or 3rd | G 900–1,000 mg/m$^2$ (Day 1, 8)<br>V 25–30 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 17%<br>67% | 4.6 M | 8.5 M |
| Chen et al (2003)[17] | 17 | II | 2nd | G 800 mg/m$^2$ (Day 1, 8, 15)<br>V 20 mg/m$^2$ (Day 1, 8, 15)<br>Every 28 days | 31.3%<br>93.8% | 4.6 M | 8.3 M |
| Park et al (2004)[23] | 38 | II | 2nd | G 1,000 mg/m$^2$ (Day 1, 8)<br>V 30 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 21%<br>76% | 3.9 M | 8.1 M |
| Ando et al (2005)[14] | 20 | I | 3rd | G 600–1,000 mg/m$^2$ (Day 1, 8)<br>V 20–25 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 0%<br>74% | 3.9 M | 6.8 M |
| Juergens et al (2007)[21] | 15 | II | 2nd | G 1,000 mg/m$^2$ (Day 1, 15)<br>V 30 mg/m$^2$ (Day 1, 15)<br>Every 28 days, 6 cycles | 0%<br>73% | 4.2 M | 9.2 M |
| Han et al (2008)[19] | 40 | Ran II | 2nd | G 900 mg/m$^2$ (Day 1, 8)<br>V 25 mg/m$^2$ (Day 1, 8)<br>Every 21 days, until PD | 13%<br>45% | 2.6 M | ND |
| Chelis et al (2010)[16] | 14 | II | 2nd or further-line setting | G 1,200 mg/m$^2$ (Day 1, 15)<br>V 30 mg/m$^2$ (Day 1, 15)<br>Every 28 days, 6 cycles | 0%<br>27% | 3 M | 4 M |
| Our study | 85 | Retro | 2nd or further-line setting | G 1,000 mg/m$^2$ (Day 1, 8)<br>V 25 mg/m$^2$ (Day 1, 8)<br>Every 21 days | 4.7%<br>30.6% | 2.1 M | 6.9 M |

**Note:** [a]PFS of patients with stable disease ~ complete remission.

**Abbreviations:** DCR, disease control rate; G, gemcitabine; M, months; ND, not described; OS, overall survival; PD, progressive disease; PFS, progression-free survival; Ran, randomized; Retro, retrospective; RR, response rate; V, vinorelbine; W, weeks.

The most important finding is that this combination regimen was not effective in response and survival benefit. Thus, we do not recommend this regimen for pretreated patients. Compared with the previous studies,[14–24] our results were similar or inferior in overall RR and disease control rate, but had remarkably shorter PFS (Table 7). Contrary to these previous studies that focused on the second-line setting and enrolled patients with better PS, 85% and 9% of our patients were in the third- or further-line and had poor PS of 3, respectively. For chemotherapy-naïve patients, this combination regimen was not inferior in response and survival to platinum-based regimens (Table 8)[9,10,19,25–30] and showed milder toxicity.[9,10,26–28] However, for patients with poor PS, ECOG PS 2, this combination regimen provided minimal effects and harmful toxicities similar to carboplatin plus paclitaxel.[29] On the other hand, our results were opposite to the latest retrospective Korean study of 40 elderly patients (age ≥65 years). Sixty percent of study participants were receiving third- or further-line treatment and 20% had ECOG PS 2, and it was concluded that this combination is an effective and tolerable salvage regimen in elderly and heavily pretreated patients, based on their results of higher RR (34.5%), longer PFS (3.1 months), and OS (10.3 months).[31]

The second important finding is that only PS at the time of introduction of this regimen was an influential predicting factor for survival. This result was consistent with the previous pooled analyses that detected poorer PS as one of the prognostic factors for survival,[32–36] but different from them in that our analysis did not detect other parameters as predictive factors. Besides continued good PS, response to previous treatment is also suggested to be a predictor of benefit from third- and fourth-line chemotherapy.[37] In addition, a longer interval between the first- and third-line chemotherapy was associated with longer OS after third-line chemotherapy.[1] We could not obtain information during the first-line chemotherapy in eleven patients, whose past charts were lost or who had transferred to our institution after front-line chemotherapy. Therefore, we did not analyze response to previous treatment.

Our study includes the following three limitations: first, our study was a single institutional and retrospective study. Although our study may not be universal, our results discouraged the conducting of prospective studies of this

**Table 8** Review of prospective studies comparing combination chemotherapy of gemcitabine and vinorelbine with platinum-based regimens

| Authors (year) | Phase | Line | N | Regimens | RR | PFS | OS |
|---|---|---|---|---|---|---|---|
| Gridelli et al (2003)[10] | III | 1st | 251 | GV | 25% | 17 W | 32 W |
| | | | 250 | CDDP + G or V | 30% | 23 W | 38 W |
| | | | | (Age <70 years) | *P*=0.30 | *P*=0.004 | *P*=0.08 |
| Laack et al (2004)[28] | III | 1st | 143 | GV | 13.0% | 19.3 W | 35.9 W |
| | | | 144 | CDDP + GV | 28.3% | 22.3 W | 32.4 W |
| | | | | | *P*=0.004 | *P*=0.35 | *P*=0.73 |
| Chen et al (2005)[25] | Ran II | 1st | 43 | GV | 23.3% | 4.1 M | 9.5 M |
| | | | 43 | CDDP + GV | 46.5% | 7.8 M | 13.1 M |
| | | | | | *P*=0.022 | *P*=0.206 | *P*=0.375 |
| Esteban et al (2006)[26] | Ran II | 1st | 57 | GV | 37% | 5.0 M | 9 M |
| | | | 57 | CDDP + GV | 47% | 5.8 M | 10 M |
| | | | | | *P*=0.5 | *P*=0.6 | *P*=0.9 |
| Yamamoto et al (2006)[30] | Ran II | 1st | 64 | GV | 21.0% | 137 D | 385 D |
| | | | 64 | CBDCA + G | 20.3% | 165 D | 432 D |
| | | | | | *P*=0.60 | *P*=0.676 | *P*=0.298 |
| Greco et al (2007)[27] | II/III | 1st | 170 | GV | 24% | 3.9 M | 10.7 M |
| | | | 167 | CBDCA + G + PTX | 25% | 6.0 M | 10.3 M |
| | | | | | *P*=ND | *P*=0.324 | *P*=0.269 |
| Han et al (2008)[19] | Ran II | 1st | 70 | GV | 26% | 4.6 M | 13.1 M |
| | | | 75 | CDDP + CPT-11 | 38% | 3.8 M | 15.9 M |
| | | | | | *P*=0.144 | *P*=0.415 | *P*=0.285 |
| Flotten et al (2012)[9] | III | 1st | 215 | GV | ND | ND | 6.3 M |
| | | | 222 | CBDCA + V | | | 7.0 M |
| | | | | | | | *P*=0.802 |
| Saito et al (2012)[29] | Ran II | 1st | 43 | GV | 20.9% | 2.7 M | 6.0 M |
| | | | 41 | CBDCA + PTX | 29.3% | 2.9 M | 5.9 M |
| | | | | (ECOG PS 2) | *P*=ND | *P*=ND | *P*=ND |

**Abbreviations:** CBDCA, carboplatin; CDDP, cisplatin; CPT-11, irinotecan; D, days; ECOG PS, European Clinical Oncology Group performance status; G, gemcitabine; M, months; ND, not described; OS, overall survival; PFS, progression-free survival; PTX, paclitaxel; Ran, randomized; RR, response rate; V, vinorelbine; W, weeks.

combination therapy for pretreated patients. Second, the lower initial dose and total dose intensity in our practice might reduce the potential efficacy of this combination therapy. Our mean initial dose of gemcitabine, approximately 800 mg/m$^2$, was similar to the recommended dose in the previous Japanese Phase I study that evaluated this combination therapy in the third-line setting.[14] Thus, our practical dose reduction might be negligible. Third, our sample size was small. Although RR varies among drugs, races and lines, the RRs of docetaxel, pemetrexed and erlotinib monotherapy for pretreated Japanese patients with NSCLC were 12.8% (N=187),[38] 18.5% (N=108),[39] and 28.3% (N=60),[40] respectively. Assuming an expected RR of 10% or 15% with a two-sided alpha of 5%, our statistical power is 43% or 88%, respectively. Fourth, there is no rationale supporting combination chemotherapy for third- or further-line NSCLC treatment. However, some oncologists dared to choose combination chemotherapy rather than monotherapy even in the third-line setting,[41–43] possibly because monotherapy strategy is reasonable on the basis of evidences but is disappointing in efficacy. An established regimen supported by prospective studies is also necessary in the third- and further-line settings.

## Conclusion

This combination was ineffective and harmful to pretreated patients with NSCLC. We do not recommend this regimen as the later-line option.

## Disclosure

The authors report no conflicts of interest in this work.

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