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ORIGINAL ARTICLE

Gemcitabine and vinorelbine in recurrent advanced non-small cell lung cancer: sequence does matter

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Summary
Purpose Gemcitabine and vinorelbine have demonstrated clinical efficacy both as single agents and in combination in patients with metastatic non-small cell lung cancer (NSCLC). This phase II trial evaluated biweekly gemcitabine and vinorelbine in NSCLC patients who have had one prior chemotherapeutic regimen and have had disease progression.
Methods Gemcitabine (1,200 mg/m^2 IV over 30 min) was followed by vinorelbine (30 mg/m^2 IV over 6–10 min) on days 1 and 15 of each 28 day cycle. Chemotherapy was given for six cycles unless disease progression or unacceptable toxicity was seen.
Results From 11/1998 to 10/2000, 15 of 20 patients enrolled (6 males, 9 females) were evaluable for response and survival. Two patients had grade 4 neutropenia, and one patient had grade 4 thrombocytopenia. The only non-hematologic grade 3 toxicities were fatigue, phlebitis, and arthralgias. No objective responses were observed, but 11 patients had stable disease for a mean of 6 months. The median survival time was 9.4 months (95% CI = 4.2, 14.8), with a median time to progression of 4.2 months (95% CI = 1.9, 5.6). The 1 year survival was 47%.
Conclusions While this schedule of gemcitabine and vinorelbine was well tolerated, it was felt to be inactive. In vitro and pharmacokinetic studies published after the completion of our trial, suggest gemcitabine followed by vinorelbine may have antagonistic effects leading to lower dose delivery of both drugs. Our study was the only study of gemcitabine and vinorelbine in second-line NSCLC in the literature without an objective response. Our study was the only second-line study that administered gemcitabine prior to vinorelbine. First-line studies in the literature that administered vinorelbine prior to gemcitabine had, on average, a 1.7 month higher median survival (10.0 vs. 8.3 mos; *P* value <0.001). Because of the lack of response, further studies using this drug sequence, dose, and schedule for gemcitabine and vinorelbine are not recommended.

Keywords Non-small cell lung cancer · Gemcitabine · Vinorelbine · Metastatic

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Introduction

At the time of diagnosis, two-thirds of patients with non-small cell lung cancer (NSCLC) will have inoperable or metastatic disease. Treatment options for most of these patients are limited to palliative chemotherapy and radiation. Platinum-based combination chemotherapy has become the mainstay of first-line therapy [1–4]. Because of the advances made in the last decade with platinum-based therapies, more patients are surviving long enough with good performance status to be offered second-line chemotherapy regimens.

In the past decade, several new chemotherapeutic drugs have been shown to have single agent efficacy in NSCLC. Multiple phase II trials have begun looking at possible combinations of these agents for use in second-line regimens. These drugs include docetaxel, paclitaxel, irinotecan, pemetrexed, gemcitabine, and vinorelbine [5]. Ideally, a combination that is appropriate for second

line would not only be efficacious, but also have a modest toxicity profile and an easy schedule of administration. Gemcitabine plus vinorelbine was felt to be one of those combinations.

Gemcitabine, is a nucleoside analog that is phosphorylated intracellularly to its active triphosphate metabolite. When gemcitabine triphosphate is incorporated into DNA, it leads to DNA chain termination, inducing apoptosis [6]. Gemcitabine has a mild toxicity profile across all age groups. The most common side effects include myelosuppression, flu-like symptoms, transient hepatic dysfunction, and rashes.

Vinorelbine is a semi-synthetic vinca alkyloid that binds to tubulin, resulting in the inhibition of microtubule formation. It is therefore able to disrupt the mitotic spindle apparatus, which is critical for cell replication [7]. Vinorelbine also has a mild toxicity profile. Myelosupression, nausea, phlebitis, and mild reversible peripheral neuropathy are the main side effects associated with vinorelbine.

When this study was designed, gemcitabine and vinorelbine were felt to be an ideal combination for use as second-line therapy for several reasons: First, the majority of patients who received first-line therapy have received combination therapy, including a platinum drug with a second agent that could, but often did not, include either of these two agents [8, 9]. Second, this combination has been shown to have a very low toxicity profile. Given the tolerability of both of these agents, the generally non-overlapping mild side effect profile, and the similar dosing schedules, gemcitabine and vinorelbine were considered optimal choices for second-line combination therapy. In this phase II trial, we have assessed the response rate of gemcitabine and vinorelbine given on a twice monthly schedule in advanced NSCLC patients who have failed one prior chemotherapy regimen.

Patients and methods

This trial was initiated in November 1998 and closed to accrual in October 2000. This was a single institution trial performed at the Johns Hopkins Sidney Kimmel Comprehensive Cancer Center in Baltimore, Maryland. This, trial was approved by the Johns Hopkins Institutional Review Board. This trial was funded through the support of Eli Lilly and Company.

Eligibility

To be eligible, patients were required to have histologically confirmed stage IV NSCLC that had progressed on one prior chemotherapeutic regimen. Eligible histologies included squamous, adenocarcinoma, large-cell carcinoma, mixed NSCLC, and NSCLC not otherwise specified. Patients with any component of small cell anaplastic histology were excluded from this study. Patients with brain metastases were eligible for participation, providing the brain metastases were stable. Patients requiring concurrent radiation therapy for any reason were excluded.

Patients with Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0, 1, or 2 over the age of 18 were eligible. Adequate organ function, including total leukocyte count $\geq$4,000/mm^3 or absolute neutrophil count (ANC) $\geq$2,000/mm^3, hemoglobin $\geq$10 g/dl, platelet count >100,000/mm^3, creatinine $\leq$2 mg/dl, bilirubin $\leq$1.5 g/dl, and SGOT (AST) and SGPT (ALT) $\leq 3\times$ the upper level of the institutional normal limit, was required. Patients were not eligible if they had any other active malignancy or if they had any serious medical or psychiatric disorder, as determined by physician discretion. Any actively infected patients were excluded. Patients with childbearing potential were required to use an effective method of contraception during the trial and for 3 months after completion of treatment. Female patients who were either pregnant or lactating were excluded. Patients had to be able to give informed consent to participation in the study.

Study evaluations

Pretreatment assessment was required within 4 weeks prior to registration and included history and physical examination, complete blood counts, comprehensive metabolic profile, chest and abdominal CT scan, and a pregnancy test if the patient was female. History and physical examination, complete blood counts, and comprehensive chemistry profiles were performed twice monthly during chemotherapy administration. Full staging, including radiographs, were repeated every 8 weeks while patients were receiving chemotherapy and then every 3 months in follow-up.

Disease assessment

Patients were required to have measurable or evaluable disease. Measurable disease could be either unidimensional or bidimensional. Bidimensional disease was preferred, if available, and was defined as a mass reproducibly measurable in two dimensions by ruler or calipers, with surface area determined by the product of the longest diameter and its greatest perpendicular diameter. Unidimensional measurements were accepted for mediastinal or hilar width or quantification of

malignant hepatomegaly. Accepted radiological modalities included plain radiography, computed tomography (CT), ultrasonography, or magnetic resonance imaging (MRI). Evaluable disease was defined as disease evident on clinical exam or radiography but not reproducibly measurable by the criteria outlined above. This included disease evident on bone scan; it also included pleural effusions or ascites that was refractory to diuretics.

Response criteria

Response was evaluated in all patients who completed at least two cycles of chemotherapy. Complete clinical response was defined as complete disappearance of all clinically detectable malignant disease for at least 4 weeks. Partial clinical response was defined as greater than or equal to 50% decrease in tumor size for at least 4 weeks without appearance of new areas of malignant disease or increase in size of any area of known malignant disease of greater than 25%. Stable disease was defined as no significant change in measurable or evaluable disease for at least 4 weeks and no appearance of new areas of malignant disease. Progression was defined as significant increase in size of lesions present at the start of therapy or after a response, or appearance of new metastatic lesions known not to be present at the start of therapy. Progression was also documented if patients had stable objective disease but also had deterioration in ECOG performance status $\geq$1 level that was related to malignancy.

Treatment methods

Each cycle of chemotherapy consisted of gemcitabine 1,200 mg/m^2 given intravenously (IV) over 30 min through a central venous line, immediately followed by vinorelbine 30 mg/m^2 given IV over 6–10 min. Both drugs were given on days 1 and 15 of each 28-day cycle. Chemotherapy was dosed on the basis of body surface area using actual body weight. Antiemetics were administered at the discretion of the investigator. Routine use of granulocyte colony stimulatory factors was discouraged.

Patients were treated with a total of up to six cycles unless they either had evidence of disease progression or unacceptable toxicity. All toxicity was graded using the National Cancer Institute Common Toxicity Criteria, version 2.0. Each new cycle was initiated only if patients had a current non-hematologic drug toxicity grade of 0–1, excluding alopecia and weight loss. Minimum ANC prior to each subsequent cycle was 2,000/mm^3, and the minimum platelet count was 100,000/mm^3. Day 15 doses were given at full dose if there was no grade 3/4 toxicity, the ANC was $\geq$1,000/mm^3, and the platelet count was $\geq$75,000/mm^3.

Dose modifications

If, on day 1 of a cycle, the ANC was <2,000/mm^3 but $\geq$1,500/mm^3 or the platelet count was <100,000/mm^3 but $\geq$75,000/mm^3, then the dose of gemcitabine was reduced to 1,000 mg/m^2, and the dose of vinorelbine was reduced to 25 mg/m^2. If the ANC was <1,500/mm^3 but $\geq$1,000/mm^3 or the platelet count was <75,000/mm^3 but $\geq$50,000/mm^3, then the dose of gemcitabine was reduced to 800 mg/m^2 and the dose of vinorelbine was reduced to 20 mg/m^2. Once the dose was modified it was not re-escalated in subsequent cycles.

If the ANC was $\leq$1,000/mm^3 or the platelet count was $\leq$50,000/mm^3, then the dose was delayed by 1 week and the dose reduced. If the ANC and/or platelets had not adequately recovered within 2 weeks, the patient was removed from the study.

Statistical design

The primary endpoint of this non-randomized phase II clinical trial was to evaluate the objective response rate of two or more cycles of gemcitabine and vinorelbine in patients with advanced NSCLC who had previously received one prior chemotherapy regimen. Secondary endpoints included evaluation of toxicity and tolerability of this dose schedule of gemcitabine and vinorelbine, as well as assessment of time to progression and overall survival of patients who completed at least two cycles of treatment.

A Simon two-stage accrual design was employed for this study [10]. Initially 15 evaluable patients were entered into the study. If one or more objective responses were seen in this initial sample, the study was to accrue an additional 20 patients, for a total accrual of 35 patients. With 35 analyzable patients, a 20% improvement in response rate could be detected above the standard response rate of 10%, which corresponds to the standard of care. The power of this study was 90% with a significance level of 5%. Survival and time to progression were determined by the method of Kaplan and Meier [11].

Results

Patient characteristics

Patient characteristics are summarized in Table 1. The median age was 60 years (range 46–75 years). Sixty-five

percent of the participants were female, and 95% of patients were Caucasian. The distribution of NSCLC histologies was typical of that in the USA [12]. Thirty-five percent of patients enrolled at a performance status of two. Twenty percent of patients who enrolled had stable brain metastases at the time of entry.

Among the 20 eligible patients, five patients (20%) received only one cycle of therapy. Of these five patients, three had a significant decline in performance status after the first cycle and two had progressive disease (including one who died from respiratory failure unrelated to the treatment). The remaining 15 patients received two or more cycles of gemcitabine and vinorelbine and were considered evaluable for response and survival for the purposes of this study. Four patients received the full course of six cycles of therapy.

Toxicities

The most common toxicities were hematologic, including two grade 4 neutropenias and one grade 4 thrombocytopenia. There were no other grade 4 toxicities. The only non-hematologic grade 3 toxicities were fatigue, phlebitis, and arthralgias. There were no dose reductions required throughout this trial. There were several treatment delays. Treatment was held for 1 week for myelosuppression in one patient. Two patients had treatment held because of infections; one patient had a catheter-related blood stream infection, and one patient had infectious colitis. One patient had treatment held for a month secondary to the need for palliative radiation therapy for pain. The chemotherapy was restarted after the completion of the radiation, but after two doses of chemotherapy she developed radiation pneumonitis so the treatment was discontinued.

Table 1 Patient characteristics

Characteristic	Number of patients (%) ($n = 20$)
Gender	
Male	7 (35)
Female	13 (65)
Race	
White	19 (95)
African American	1 (5)
Age	
40–49	2 (10)
50–59	8 (40)
60–69	7 (35)
70–79	3 (15)
ECOG performance status	
1	13 (65)
2	7 (35)
Histology	
Adenocarcinoma	11 (55)
Squamous carcinoma	5 (25)
Poorly differentiated NSCLC	4 (20)
Presence of brain metastases	
Diagnosed prior to enrollment	4 (20)

ECOG Eastern Cooperative Oncology Group; *NSCLC* Non-small cell lung cancer

Efficacy

There were no partial or complete responses among the 15 evaluable patients on this study. This study was therefore closed to accrual after enrollment of the initial 15 evaluable patients. Eleven patients had stable disease for two or more cycles. Three of those patients had stable disease at the completion of the full six cycles of chemotherapy. The average duration of stable disease was 6 months. The median survival time was 9.4 months (95% CI = 4.2, 14.8), with a median time to progression of 4.2 months (95% CI = 1.9, 5.6). The 1 year survival was 47%.

Discussion

Our current schedule of gemcitabine and vinorelbine, although well tolerated, was found to be ineffective. Despite our lack of objective responses, the median survival in the evaluable patients in this study was quite good. The high rate of disease stabilization may account in part for the median survival of 9.4 months we observed. Additionally, studies demonstrating survival benefit for patients with relapsed NSCLC from chemotherapy agents in the second-line setting were being presented and published while our study was being conducted. Over half of the patients on our study subsequently received third or fourth-line chemotherapy after coming off trial, which previously was not standard practice.

There may be several explanations for the lack of objective response shown in this trial. The first aspect of this trial that differed from previous second-line trials is the treatment schedule (Table 2). Dosing consecutively on days 1 and 8 or on days 1, 8, and 15 may achieve a dose threshold that our dose and schedule could not reach. The day 1 and 15 schedule with our dose choice may allow time for either tumor regrowth between doses or promote drug resistance in the tumor cells by not taking advantage of sequential therapy.

This hypothesis is supported by a phase I dose-finding study that was performed after the completion of our trial [13]. This study by Castellano and colleagues inves-

Table 2 Published regimens with gemcitabine and vinorelbine in the second-line

Reference	Gemcitabine dose (mg/m^2)	Vinorelbine dose (mg/m^2)	Sequence	Number of evaluable patients	Response rate (%)	Median survival (months)
Current study 2006	1,200 Days 1,15	30 Days 1,15	G–V	15	0	9.4
Park [24] 2004	1,000 Days 1,8	30 Days 1,8	V–G	38	21	8.1
Chen [20] 2003	800 Days 1,8,15	20 Days 1,8,15	V–G	17	31.3	8.3
Herbst [22] 2002	1,000 900 Days 1,8,15	30 25 Days 1,8,15	V–G	Dose 1: 4 Dose 2: 32 Total: 36	17	8.5
Kosmas [23] 2001	1,000 Days 1,8	25 Days 1,8	V–G	40	22.5	7
Hainsworth [21] 2000	1,000 Days 1,8,15	20 Days 1,8,15	V–G	50	18	6.5
Camps [19] 2000	1,200 Days 1,8,15	25 Days 1,8	NS	16	6.25	6.2

G gemcitabine, *V* vinorelbine, *NS* not stated

tigated the optimal dosing regimen for a biweekly administration schedule for gemcitabine and vinorelbine in advanced solid tumors. One quarter of the patients in this study had NSCLC. The recommended dose for vinorelbine (30 mg/m^2) was equal to the dose chosen for our study, but the optimal dose determined for gemcitabine (2,500 mg/m^2) was double the dose used in our study. The Castellano study also used a fixed-dose infusion rate for gemcitabine. This administration regimen attempts to increase the amount of active gemcitabine delivered to the patient by slowing the infusion rate allowing more drug to be phosphorylated by deoxycytidine kinase [14]. This further underscores the concept that a more optimal dose of gemcitabine could have been delivered to the patients in our study.

The next part of our trial that differs from many of the others was the sequence chosen for delivery of the chemotherapy (Tables 2, 3). When the majority of studies of gemcitabine and vinorelbine were designed, the preclinical data did not suggest inferiority for either sequence [15]. Many studies cited that vinorelbine was given prior to gemcitabine because vinorelbine is a known vesicant. Our study used central venous catheters for chemotherapy administration to minimize patient risk from vinorelbine. We also chose to administer the gemcitabine first. This sequencing difference may have played a clinically significant role.

Preclinical data on the combination of gemcitabine and vinorelbine over the last 10 years have been conflicting. An early study, published by Budman and colleagues in 1998, utilized breast cancer cell lines [16]. The results of this study suggested that gemcitabine and vinorelbine, administered either simultaneously or sequentially to tumor cells in vitro may have antagonistic effects. Further work by Herbst and colleagues [15] assessed synergy in Lewis lung carcinoma mouse models. These experiments documented additive effects from gemcitabine and vinorelbine except at the highest gemcitabine dose studied. The poorer outcome at the highest gemcitabine dose may have been due to toxicity or antagonism. Further in vitro studies were performed in lung cancer cell lines after the publication of results of a phase III trial comparing single-agent gemcitabine and single-agent vinorelbine to the combination of gemcitabine and vinorelbine in the elderly. No benefit was shown from use of the combination over single agents, in this study by Gridelli and colleagues [17]. The in vitro lung cancer cell line study results were similar to the data presented by Dr. Budman; two of three cell lines treated with gemcitabine prior to vinorelbine and all three cell lines exposed to vinorelbine followed by gemcitabine showed antagonistic effects.

Based on the observation that response rate may vary by sequence, Cattel and colleagues [18] performed a pharmacokinetic study assessing the sequence of gemcitabine and vinorelbine delivery in advanced solid tumors. This study found that the maximal concentration and the total area under the curve (AUC) of gemcitabine in patients given vinorelbine prior to gemcitabine was 20% higher than when gemcitabine was administered first. The vinorelbine maximal concentration was 30% higher when vinorelbine was administered as the first drug. This study also found that vinorelbine total AUC was over three times lower on average in this study when given in combination than in other pharmacokinetic studies in which

Table 3 Published regimens with gemcitabine and vinorelbine in the first-line

Reference	Gemcitabine dose (mg/m^2)	Vinorelbine dose (mg/m^2)	Sequence	Number of evaluable patients	Response rate (%)	Median survival (months)
Katakami [32] 2003	1,000 Days 1,8	25 Days 1,8	V–G	50	18	13.9
Esteban [28] 2002	1,250 Days 1,8	30 Days 1,8	V–G	41	39	9
Herbst [22] 2002	1,000 900 Days 1,8,15	30 25 Days 1,8,15	V–G	Dose 1: 4 Dose 2: 38 Total: 42	36	10.1
Baron [26] 2001	1,000 Days 1,8,15	25 Days 1,8,15	G–V	38	29	8.5
Hirsh [30] 2001	1,000 1,000 Days 1,8,15	25 30 Days 1,8,15	G–V	Dose 1: 15 Dose 2: 19 Total: 34	53	11.1
Laack [35] 2001	1,000 Days 1,8,15	30 Days 1,8,15	G–V	70	41	8.3
Palmeri [38] 2001	1,000 Days 1,8,15	30 Days 1,8	V–G	45	40	8
Bajetta [25] 2000	1,250 Days 1,8	25 Days 1,8	NS	54	30	12
Chen [27] 2000	800 Days 1,8,15	20 Days 1,8,15	V–G	40	72.5	11
Gridelli [29] 2000	1,000 1,200 1,000 Days 1,8	25 25 30 Days 1,8	G–V	Dose 1: 43 Dose 2: 42 Dose 3: 41 Total: 126	27.9 21.4 29.3	7.6
Krajnik [34] 2000	1,200 Days 1,8,15	25 Days 1,8,15	V–G	78	19	7
Lilenbaum [36] 2000	1,000 1,250 Days 1,8	25 25 Days 1,8	G–V	Dose 1: 6 Dose 2: 26 Total: 32	25	8.3
Lorusso [37] 2000	1,200 Days 1,8	30 Days 1,8	V–G	52	36	12.5
Isokangas [31] 1999	1,200 Days 1,15	35 Days 1,15	NS	28	46	8
Krajnik [33] 1998	Phase I 600–1,200 Days 1,8,15	Phase I 10–30 Days 1,8,15	V–G	31	23	NR

G gemcitabine, *V* vinorelbine, *NR* not reported, *NS* not stated

vinorelbine is given as a single agent. Therefore when patients are administered gemcitabine followed by vinorelbine, they are receiving lower doses of both agents than if the order were reversed.

This concept can be demonstrated by looking at the trials published which combine gemcitabine and vinorelbine. In the second-line setting, our trial was the only study that documented administration of gemcitabine before vinorelbine (Table 2) [19–24]. Our study was also the only study that had no objective responses. In the first-line setting, the majority of trials administered vinorelbine first (Table 3) [22, 25–38]. Because almost all of the trials of gemcitabine and vinorelbine are single-arm phase 2 trials, formal meta-analysis techniques could not be applied to combine the data. We performed a single-arm weighted analysis of all the first-line studies stratified by sequence order. Each study included in the analysis was weighted by the sample size of the study. In this analysis, the median survival of patients treated with gemcitabine first was 8.3 months. The median survival of the patients treated with vinorelbine first was 10.0 months. This difference in median survivals is clinically and statistically significant (P value <0.001). The studies of this combination in the elderly also show similar impact from drug sequence (Table 4) [17, 39–43]. The most compelling study in the elderly is by Gridelli and colleagues [17]. This study randomized patients to single-agent gemcitabine, single-agent vinorelbine, or the combination with gemcitabine given first. This study found no significant difference between the combination and either single agent arm (P values >0.5).

Table 4 Published regimens with gemcitabine and vinorelbine in the elderly or patients with poor performance-status

Reference	Gemcitabine dose (mg/m^2)	Vinorelbine dose (mg/m^2)	Sequence	Number of evaluable patients	Response rate (%)	Median Survival (months)
Kimura H [43] 2004	1,000 Days 1,15	25 Days 1,15	NS	40	27.5	13
Chen YM [40] 2003	800 Days 1,8,15	20 Days 1,8,15	V–G	19	65	10
Gridelli C [17] 2003	1,200 – 1,000 Days 1,8	– 30 25 Days 1,8	G–V	233 233 232 Total: 698	16 18 21	6.5 8.3 6.9
Beretta GD [39] 2000	1,000 Day 1,8	25 Day 1,8	G–V	40	35	8
Frasci G [42] 2000	– 1,200 Days 1,8	30 30 Days 1,8	NS	60 60 Total: 120	15 22	4.5 7.3
Feliu J [41] 1999	1,000 Days 1,8,15	25 Days 1,8,15	NS	49	26	NR

G gemcitabine, *V* vinorelbine, *NR* not reported, *NS* not stated

The importance of sequence of administration of chemotherapeutic agents has become more evident in the last 10 years. Some interactions now are well known such as the pharmacokinetic differences seen when the sequence of paclitaxel and cisplatin are reversed [44]. Others are currently being explored. Gemcitabine, pemetrexed, vinorelbine, paclitaxel, docetaxel, and topotecan are just a few of the agents that have documented differences in not only pharmacokinetics but also toxicity based on sequence of administration [18, 45–49].

Conclusion

Very few agents have shown objective responses in the second-line setting for NSCLC. Currently, only three agents, docetaxel and, recently, pemetrexed and erlotinib, have gained approval of the Food and Drug Administration for this indication [50–52]. The overall response rate of these agents is approximately 10%. The combination of gemcitabine and vinorelbine has shown promise. From the review of the literature of this combination, it is suggestive that survival may be impacted by the sequence of drug administration. From the data we have, in the second-line setting, the best regimen is dosed with vinorelbine given before gemcitabine on days 1 and 8, given the high percentage of patients in trials who could not receive chemotherapy on day 15 because of hematologic toxicity.

In conclusion, non-platinum-based regimens, such as gemcitabine and vinorelbine, appear to be active in the second-line setting, but not at the dosing and schedule utilized in this trial.

Conflicts of interest

Drs. Juergens and Brahmer have no financial conflicts of interest to list in regard to this publication. Dr. Ettinger is a consultant and receives research support from Eli Lilly and Company and Glaxo Smith Klein.

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References

1. Ettinger DS (2002) Is there a preferred combination chemotherapy regimen for metastastic non-small cell lung cancer? Oncologist 7:226–233
2. Grilli R, Oxman AD, Julian JA (1993) Chemotherapy for advanced non-small-cell lung cancer: how much benefit is enough? J Clin Oncol 11:1866–1872
3. Marino P, Pampallona S, Preatoni A, Cantoni A, Invernizzi F (1994) Chemotherapy vs supportive care in advanced non-small-cell lung cancer. Results of a meta-analysis of the literature. Chest 106:861–865
4. Souquet PJ, Chauvin F, Boissel JP, Cellerino R, Cormier Y, Ganz PA, Kaasa S, Pater JL, Quoix E, Rapp E (1993) Polychemotherapy in advanced non small cell lung cancer: a meta-analysis. Lancet 342:19–21
5. Bunn PA Jr, Kelly K (1998) New chemotherapeutic agents prolong survival and improve quality of life in non-small cell lung cancer: a review of the literature and future directions. Clin Cancer Res 4:1087–1100
6. Plunkett W, Huang P, Xu YZ, Heinemann V, Grunewald R, Gandhi V (1995) Gemcitabine: metabolism, mechanisms of action, and self-potentiation. Semin Oncol 22:3–10
7. Johnson SA, Harper P, Hortobagyi GN, Pouillart P (1996) Vinorelbine: an overview. Cancer Treat Rev 22:127–142
8. Fossella F, Pereira JR, von Pawel J, Pluzanska A, Gorbounova V, Kaukel E, Mattson KV, Ramlau R, Szczesna A, Fidias P, Millward M, Belani CP (2003) Randomized, multinational, phase III study of docetaxel plus platinum combinations ver-

sus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 Study Group. J Clin Oncol 21:3016–3024
9. Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH, the Eastern Cooperative Oncology Group (2002) Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. N Engl J Med 346:92–98
10. Simon R (1989) Optimal two-stage designs for phase II clinical trials. Control Clin Trials 10:1–10
11. Kaplan E, Meier P (1958) Nonparametric estimation grom incomplete observations. J Am Stat Assoc 53:457–481
12. Jemal A, Murray T, Ward E, Samuels A, Tiwari RC, Ghafoor A, Feuer EJ, Thun MJ (2005) Cancer statistics, 2005. CA Cancer J Clin 55:10–30
13. Castellano D, Hitt R, Ciruelos E, Cortes-Funes H, Colomer R (2003) Biweekly vinorelbine and gemcitabine: a phase I dose-finding study in patients with advanced solid tumors. Ann Oncol 14:783–787
14. Tempero M, Plunkett W, Ruiz van Haperen V, Hainsworth J, Hochster H, Lenzi R, Abbruzzese J (2003) Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma. J Clin Oncol 21:3402–3408
15. Herbst RS, Lynch C, Vasconcelles M, Teicher BA, Strauss G, Elias A, Anderson I, Zacarola P, Dang NH, Leong T, Salgia R, Skarin AT (2001) Gemcitabine and vinorelbine in patients with advanced lung cancer: preclinical studies and report of a phase I trial. Cancer Chemother Pharmacol 48:151–159
16. Budman DR, Calabro A, Kreis W (1998) In vitro evaluation of synergism or antagonism with combinations of new cytotoxic agents. Anticancer Drugs 9:697–702
17. Gridelli C, Perrone F, Gallo C, Cigolari S, Rossi A, Piantedosi F, Barbera S, Ferrau F, Piazza E, Rosetti F, Clerici M, Bertetto O, Robbiati SF, Frontini L, Sacco C, Castiglione F, Favaretto A, Novello S, Migliorino MR, Gasparini G, Galetta D, Iaffaioli RV, Gebbia V (2003) Chemotherapy for elderly patients with advanced non-small-cell lung cancer: the Multicenter Italian Lung Cancer in the Elderly Study (MILES) phase III randomized trial. J Natl Cancer Inst 95:362–372
18. Cattel L, Airoldi M, Passera R, Cagliero E, Stella B, Goffredo F (2004) Gemcitabine plus vinorelbine chemotherapy regimens: a pharmacokinetic study of alternate administration sequences. Pharm World Sci 26:238–241
19. Camps C, Martinez EN, Jaime AB (2000) Second-line treatment with gemcitabine and vinorelbine in non-small-cell lung cancer (NSCLC) cisplatin failures: a pilot study. Lung Cancer 27:47–53
20. Chen YM, Perng RP, Lee CS, Lin WC, Tsai CM, Whang-Peng J (2003) Phase II study of gemcitabine and vinorelbine combination chemotherapy in patients with non-small-cell lung cancer not responding to previous chemotherapy. Am J Clin Oncol 26:567–570
21. Hainsworth JD, Burris HA III, Litchy S, Erland JB, Hon JK, Brierre JE, Greco FA (2000) Gemcitabine and vinorelbine in the second-line treatment of nonsmall cell lung carcinoma patients: a minnie pearl cancer research network phase II trial. Cancer 88:1353–1358
22. Herbst RS, Khuri FR, Lu C, Liu DD, Fossella FV, Glisson BS, Pisters KM, Shin DM, Papadimitrakopoulou VA, Kurie JM, Blumenschein G Jr, Kies MS, Zinner R, Jung MS, Lu R, Lee JJ, Munden RF, Hong WK, Lee JS (2002) The novel and effective nonplatinum, nontaxane combination of gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: potential for decreased toxicity and combination with biological therapy. Cancer 95:340–353
23. Kosmas C, Tsavaris N, Panopoulos C, Vadiaka M, Stavroyianni N, Kourelis T, Malamos N, Antonopoulos M, Kalofonos HP (2001) Gemcitabine and vinorelbine as second-line therapy in non-small-cell lung cancer after prior treatment with taxane+platinum-based regimens. Eur J Cancer 37:972–978
24. Park YH, Lee JC, Kim CH, Ryoo BY, Kim HT (2004) Gemcitabine and vinorelbine as second-line therapy for non-small cell lung cancer after treatment with paclitaxel plus platinum. Jpn J Clin Oncol 34: 245–249
25. Bajetta E, Chiara SS, De CD, Bidoli P, Mariani L, Zilembo N, Pozzi P, Procopio G (2000) Gemcitabine plus vinorelbine as first-line chemotherapy in advanced nonsmall cell lung carcinoma a phase II trial. Cancer 89:763–768
26. Baron F, Cueva J, Grana B, Curiel T, Leon L, Vazquez F, Candamio S, Lopez R (2001) Gemcitabine plus vinorelbine for the treatment of advanced non-small cell lung cancer. Eur J Cancer 37:1381–1384
27. Chen YM, Perng RP, Yang KY, Liu TW, Tsai CM, Ming-Liu J, Whang-Peng J (2000) A multicenter phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (Stage IIIB/IV) non-small cell lung cancer. Chest 117:1583–1589
28. Esteban E, Fra J, Corral N, Valle M, Carrasco J, Sala M, Puerta J, Estrada E, Palacio I, Vieitez JM, Buesa JM, Lacave AJ (2002) Phase I/II study of gemcitabine plus vinorelbine in non-small cell lung cancer. Invest New Drugs 20:73–82
29. Gridelli C, Frontini L, Perrone F, Gallo C, Gulisano M, Cigolari S, Castiglione F, Robbiati SF, Gasparini G, Ianniello GP, Farris A, Locatelli MC, Felletti R, Piazza E (2000) Gemcitabine plus vinorelbine in advanced non-small cell lung cancer: a phase II study of three different doses. Gem Vin Investigators. Br J Cancer 83:707–714
30. Hirsh V, Langleben A, Ayoub J, Cormier Y, Pintos J, Iglesias JL (2001) Flexible chemotherapy regimen with gemcitabine and vinorelbine for metastatic nonsmall cell lung carcinoma: a phase II multicenter trial. Cancer 92: 830–835
31. Isokangas OP, Knuuttila A, Halme M, Mantyla M, Lindstrom I, Nikkanen V, Viren M, Joensuu H, Mattson K (1999) Phase II study of vinorelbine and gemcitabine for inoperable stage IIIB-IV non-small-cell lung cancer. Ann Oncol 10:1059–1063
32. Katakami N, Sugiura T, Nogami T, Yamamoto H, Negoro S, Nakano T, Okamoto N, Takada Y, Kodama K, Ariyoshi Y (2004) Combination chemotherapy of gemcitabine and vinorelbine for patients in stage IIIB-IV non-small cell lung cancer: a phase II study of the West Japan Thoracic Oncology Group (WJTOG) 9908. Lung Cancer 43:93–100
33. Krajnik G, Wein W, Greil R, Marhold F, Mohn-Staudner A, Kummer F, Malayeri R, Zochbauer-Muller S, Huber H, Pirker R (1998) Vinorelbine/gemcitabine in advanced non-small cell lung cancer (NSCLC): a phase I trial. Eur J Cancer 34:1977–1980
34. Krajnik G, Mohn-Staudner A, Thaler J, Greil R, Schmeikal S, Marhold F, Deutsch J, Preiss P, Malayeri R, Schafer-Prokop C, Wein W, Huber H, Pirker R (2000) Vinorelbine-gemcitabine in advanced non-small-cell lung cancer (NSCLC): an AASLC phase II trial. Austrian Association for the Study of Lung Cancer. Ann Oncol 11:993–998
35. Laack E, Mende T, Benk J, Chemaissani A, Scholtze J, Lorenz C, Niestroy A, Dalhoff K, Muller T, Walter T, Durk H, Edler L, Hossfeld DK (2001) Gemcitabine and vinorelbine as first-line chemotherapy for advanced non-small cell lung cancer: a phase II trial. Eur J Cancer 37:583–590
36. Lilenbaum R, Cano R, Schwartz M, Siegel L, Lutzky J, Lewis M, Krill E, Barreras L, Davila E (2000) Gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: a phase II study. Cancer 88:557–562

37. Lorusso V, Carpagnano F, Frasci G, Panza N, Di RG, Cisternino ML, Napoli G, Orlando S, Cinieri S, Brunetti C, Palazzo S, De LM (2000) Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small-cell lung cancer. J Clin Oncol 18:405–411
38. Palmeri S, Leonardi V, Gebbia V, De Bella MT, Ferrau F, Faillu G, Spatafora M, Valenza R, Di VG, Vitello S, Carroccio R, Sciortino G, Vaglica M, Accurso V, Agostara B, Licata G (2001) Gemcitabine plus vinorelbine in stage IIIB or IV non-small cell lung cancer (NSCLC): a multicentre phase II clinical trial. Lung Cancer 34:115–123
39. Beretta GD, Michetti G, Belometti MO, Gritti G, Quadri A, Poletti P, Labianca R (2000) Gemcitabine plus vinorelbine in elderly or unfit patients with non-small cell lung cancer. Br J Cancer 83:573–576
40. Chen YM, Perng RP, Chen MC, Tsai CM, Ming-Liu J, Whang-Peng J (2003) A phase II trial of vinorelbine plus gemcitabine in previously untreated inoperable (stage IIIb/IV) non-small-cell lung cancer patients aged 80 or older. Lung Cancer 40:221–226
41. Feliu J, Lopez GL, Madronal C, Espinosa E, Espinosa J, Giron CG, Martinez B, Castro J, De lG I, Baron MG (1999) Gemcitabine plus vinorelbine in nonsmall cell lung carcinoma patients age 70 years or older or patients who cannot receive cisplatin. Oncopaz Cooperative Group. Cancer 86:1463–1469
42. Frasci G, Lorusso V, Panza N, Comella P, Nicolella G, Bianco A, De CG, Iannelli A, Bilancia D, Belli M, Massidda B, Piantedosi F, Comella G, De LM (2000) Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18:2529–2536
43. Kimura H, Kasahara K, Shibata K, Shirasaki H, Iwasa K, Yoshimoto A, Kita T, Fuzimura M, Nakao S (2004) A phase II trial of biweekly administration of vinorelbine (V) and gemcitabine (G) in elderly patients (Pts) with advanced non-small cell lung cancer (NSCLC) (meeting abstracts). J Clin Oncol 22:7331
44. Rowinsky EK, Gilbert MR, McGuire WP, Noe DA, Grochow LB, Forastiere AA, Ettinger DS, Lubejko BG, Clark B, Sartorius SE (1991) Sequences of taxol and cisplatin: a phase I and pharmacologic study. J Clin Oncol 9:1692–1703
45. Adjei AA, Erlichman C, Sloan JA, Reid JM, Pitot HC, Goldberg RM, Peethambaram P, Atherton P, Hanson LJ, Alberts SR, Jett J (2000) Phase I and pharmacologic study of sequences of gemcitabine and the multitargeted antifolate agent in patients with advanced solid tumors. J Clin Oncol 18: 1748–1757
46. Cattel L, Recalenda V, Airoldi M, Tagini V, Arpicco S, Brusa P, Bumma C (2001) A sequence-dependent combination of docetaxel and vinorelbine: pharmacokinetic interactions. Farmaco 56: 779–784
47. de Jonge MJA, Loos WJ, Gelderblom H, Planting ASTh van der Burg MEL, Sparreboom A, Brouwer E, van Beurden V, Mantel MA, Doyle E, Hearn S, Ross G, Verweij J (2000) Phase I pharmacologic study of oral topotecan and intravenous cisplatin: sequence-dependent hematologic side effects. J Clin Oncol 18: 2104–2115
48. Dumez H, Louwerens M, Pawinsky A, Planting AS, de Jonge MJ, Van Oosterom AT, Highley M, Guetens G, Mantel M, de BG, de BE, Verweij J (2002) The impact of drug administration sequence and pharmacokinetic interaction in a phase I study of the combination of docetaxel and gemcitabine in patients with advanced solid tumors. Anticancer Drugs 13:583–593
49. Rowinsky EK, Gilbert MR, McGuire WP, Noe DA, Grochow LB, Forastiere AA, Ettinger DS, Lubejko BG, Clark B, Sartorius SE (1991) Sequences of taxol and cisplatin: a phase I and pharmacologic study. J Clin Oncol 9: 1692–1703
50. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De MF, von PJ, Gatzemeier U, Tsao TC, Pless M, Muller T, Lim HL, Desch C, Szondy K, Gervais R, Shaharyar, Manegold C, Paul S, Paoletti P, Einhorn L, Bunn PA Jr (2004) Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 22:1589–1597
51. Shepherd FA, Dancey J, Ramlau R, Mattson K, Gralla R, O'Rourke M, Levitan N, Gressot L, Vincent M, Burkes R, Coughlin S, Kim Y, Berille J (2000) Prospective randomized trial of docetaxel versus best supportive care in patients with non-small-cell lung cancer previously treated with platinum-based chemotherapy. J Clin Oncol 18:2095–2103
52. Shepherd FA, Rodrigues PJ, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van KM, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabarbara P, Seymour L (2005) Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123–132