Phase II Study of Weekly Gemcitabine and Vinorelbine for Children With Recurrent or Refractory Hodgkin's Disease: A Children's Oncology Group Report

Peter D. Cole, Cindy L. Schwartz, Richard A. Drachtman, Pedro A. de Alarcon, Lu Chen, and Tanya M. Trippett

From the Children's Oncology Group, Arcadia, CA.

Submitted October 27, 2008; accepted December 12, 2008; published online ahead of print at www.jco.org on February 17, 2009.

Supported by National Cancer Institute Grant No. CA98543. P.D.C. is a Damon Runyon-Lilly Clinical Investigator, supported in part by the Damon Runyon Cancer Research Foundation (CI-16-03).

This study has been presented in part as a poster presentation, at the American Society of Hematology Annual Meeting, December, 2007.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

Clinical Trials repository link available on JCO.org.

Corresponding author: Peter D. Cole, MD, Albert Einstein College of Medicine, Montefiore Medical Center, 111 East 210 St, Bronx, NY 10467; e-mail: pcole@aecom.yu.edu.

© 2009 by American Society of Clinical Oncology

0732-183X/09/2709-1456/\$20.00

DOI: 10.1200/JCO.2008.20.3778

ABSTRACT

Purpose

The Children's Oncology Group conducted this phase II study to assess the efficacy and toxicity of gemcitabine and vinorelbine (GV) in pediatric patients with heavily pretreated relapsed/refractory Hodgkin's disease. Both agents have significant single-agent response rates in this setting.

Methods

GV was given on days 1 and 8 of each 21-day treatment cycle: vinorelbine 25 mg/m²/dose administered via intravenous (IV) push before gemcitabine 1,000 mg/m²/dose IV over 100 minutes. Any patients who demonstrated a measurable response (complete response [CR], very good partial response [VGPR], or partial response [PR]) were considered to have experienced a response to GV. Response was evaluated after every two cycles. A two-stage minimax rule was used to test the null hypothesis that the response rate is $\leq 40\%$ against an alternative hypothesis of a response rate more than 65%.

Results

Thirty eligible patients with a median age of 17.7 years (range, 10.7 to 29.4 years) were enrolled. All patients had received at least two prior chemotherapy regimens, and 17 patients had undergone prior autologous stem-cell transplantation. Hematologic toxicity was predominant in all treatment cycles. Nonhematologic grade 3 to 4 toxicity, including elevated hepatic enzymes and hyperbilirubinemia, was less common. Pericardial and pleural effusions developed in one patient after cycles 4 and 5 of GV, consistent with gemcitabine-induced radiation recall. There were no toxic deaths. Measurable responses were seen in 19 (76%) of 25 assessable patients (95% exact binomial CI, 55% to 91%), including six CRs, 11 VGPRs, and two PRs.

Conclusion

GV is an effective and well-tolerated reinduction regimen for children with relapsed or refractory Hodgkin's disease.

J Clin Oncol 27:1456-1461. © 2009 by American Society of Clinical Oncology

INTRODUCTION

Long-term disease-free survival is low for patients with early recurrence or treatment-refractory Hodgkin's disease (HD). High-dose therapy with autologous stem-cell transplantation (ASCT) is now an accepted approach for this population that may improve long-term outcomes,¹⁻³ especially when a complete response (CR) can be achieved with reinduction therapy.⁴ Prior cytoreduction regimens have typically included alkylators and/or epipodophyllotoxins, which are associated with significant treatment-related toxicity and have been implicated as causes of secondary malignancies. This study was designed to evaluate a novel reinduction approach.

Gemcitabine is a deoxycytidine analog that inhibits DNA synthesis and repair.⁵ Two pediatric phase 1 studies of gemcitabine for patients with solid tumors or hematologic malignancies defined a maximum-tolerated dose of 1,200 mg/m²/wk for 3 weeks. In phase II trials of gemcitabine as a single agent for patients with HD, overall response rates have been as high as 39% to 43%.^{6,7} Vinorelbine, a semi-synthetic vinca alkaloid, interferes with the polymerization of tubulin. Vinorelbine is more selective for mitotic microtubules, relative to neuronal microtubules, than the other vinca alkaloids, leading to decreased peripheral neurotoxicity.⁸ Response rates as high as 50% have been reported when vinorelbine is

given weekly as a single agent to heavily pretreated patients with relapsed or refractory HD,⁹⁻¹¹ with some CRs seen.

Preclinical models have demonstrated additive activity between gemcitabine and vinorelbine, with little increased toxicity over a wide range of doses.¹² The clinical use of this combination exploits the nonoverlapping mechanisms of action and toxicity. The combination of gemcitabine plus vinorelbine (GV) has been well-tolerated by adults with non-small-cell lung cancer¹³⁻³⁰ and breast cancer³¹⁻³⁷ in weekly for 2 weeks or weekly for 3 weeks dose schedules, although the majority of these patients were chemotherapy-naïve. This protocol was designed to test the toxicity and efficacy of this drug combination among heavily pretreated pediatric patients with refractory or recurrent HD.

METHODS

Enrollment

Pediatric patients with relapsed or primary refractory HD who had been previously treated with at least two chemotherapeutic regimens were enrolled between January 2005 and April 2007. Eligibility criteria also included the following (1): age younger than 30 years; (2) radiographically measurable disease; (3) Karnofsky performance status of 0, 1, or 2; (4) recovery from the toxic effects of prior therapies; (5) life expectancy more than 8 weeks; and (6) adequate bone marrow, renal, hepatic, and pulmonary function. Patients were allowed to have received either gemcitabine or vinorelbine in the past, but those who received GV in combination therapy were excluded. Pregnant or lactating women were excluded. Informed consent was obtained from the patient or guardian in accordance with institutional policies and as approved by the US Department of Health and Human Services and in accordance with the Declaration of Helsinki.

Study Design and Treatment

This was a nonrandomized, single-arm study. Each 21-day cycle of GV included vinorelbine (25 mg/m²/dose, administered intravenously over 6 to 10 minutes) and gemcitabine (1,000 mg/m²/dose administered intravenously over 100 minutes) on days 1 and 8, followed by granulocyte colony-stimulating factor (5 µg/kg/dose) daily starting on day 9. Granulocyte colony-stimulating factor was continued for a minimum of 7 days and until the absolute neutrophil count exceeded 1,500 cells/µL.

Infusion of gemcitabine over 100 minutes was mandated on this protocol, because the cellular accumulation of the active metabolite, dFdCTP, is saturated at plasma concentrations greater than 10 to 20 micromolar,^{38,39} a concentration that is exceeded at infusion rates greater than 10 mg/m²/min.^{38,40} Prolonged infusions were well-tolerated in earlier studies⁴¹⁻⁴⁶ and may provide increased clinical benefit over bolus administration.⁴⁷

Response Evaluation

Response was assessed at the end of every two 21-day cycles. Patients with a measurable response at any time were given the option of coming off treatment to proceed directly to a stem-cell transplantation protocol. Patients with stable disease (SD) after the first two cycles were expected to continue for a minimum of four total cycles. Patients who had SD and were given fewer than four cycles were considered unassessable for disease response but were included in analysis of toxicity.

Response criteria were adapted from the criteria from the Cotswolds Meeting, the International Workshop to Standardize Response Criteria for Non-Hodgkin's Lymphomas, and the Response Evaluation Criteria in Solid Tumors.^{48,49} Briefly, CR was defined by gallium or [¹⁸F]fluorodeoxyglucose positron emission tomography (FDG-PET) negativity, at least 80% reduction in the product of the perpendicular diameters (PPD) of each site of measurable disease or return to normal size, and resolution of palpable lymphadenopathy and all focal lesions of the liver or spleen. Very good partial response (VGPR) required at least 60% reduction in the PPD of each nodal mass. Partial re-

sponse (PR) required at least 50% reduction in the PPD of each area of measurable disease. Progressive disease (PD) was defined as at least 50% increase in the PPD of any involved site or new lesions. SD was defined as less than a PR, but without meeting criteria for PD. Best response was defined as the single best response at any evaluation. Patients were defined as responders to GV if they achieved a PR, VGPR, or CR. Nonresponders included those with SD or PD.

Statistical Analysis

The primary end points were toxicity and measurable response rate. A two-stage minimax rule was used to test the null hypothesis that the true response rate was less than or equal to 40% against an alternative hypothesis of a true response rate of 65%, with 5% type 1 error and 80% power. A planned interim analysis of response data occurred after the first 12 assessable patients, and the study would have been stopped if five or fewer responses were observed. Observing 15 or more responses among a total planned accrual of 26 assessable patients would allow rejection of the null hypothesis.

The primary end points for interim safety monitoring were toxic death or presence of noncardiogenic pulmonary edema (NCPE). The maximum acceptable rate for either was defined as 5%. Operationally, $\geq$ two of 20 toxic deaths would have been considered unacceptable; this rule would have been satisfied 26% of the time for a toxic death rate of 5% and 93% of the time for a toxic death rate of 20%. Monitoring of NCPE used a Bayesian rule. Compelling evidence that the NCPE rate P exceeded 5% was defined as a posterior probability more than 80% using a β prior with mean 10% and 87.3% of support with $P < .20$. This rule would have been satisfied if $\geq$ two of eight, $\geq$ three of 19, or $\geq$ four of 26 patients experienced NCPE. An occurrence of two or more cases of NCPE of 26 patients would have resulted in an exact lower 95% confidence bound of more than 1% on the rate of NCPE. The first toxic death or the second case of NCPE at any time would have resulted in a review of all patients.

RESULTS

Patients

Thirty-three patients enrolled between January 2005 and April 2007. Three were found to be ineligible: one had been treated with only a single prior chemotherapy regimen, and two had not completed the entry requirements within 1 week before study entry. All eligible patients had been treated with a minimum of two prior chemotherapy regimens before entry on AHOD0321. Characteristics of the 30 eligible patients are listed in Table 1.

Treatment

A total of 130 21-day cycles of GV were given to the 30 eligible patients (median, five cycles; maximum, 15 cycles). Three patients continued treatment for more than 10 months from the time of study enrollment.

Five patients were unassessable for response. Three patients had SD after two cycles and chose to undergo ASCT plantation rather than proceeding to cycles 3 and 4, as mandated by the protocol. Two patients were taken off study before their first response evaluation because thrombocytopenia (platelet counts between 50,000 and 60,000/µL) delayed the start of their second cycle of therapy.

Toxicity

The incidence of grade 3 or 4 toxicity during the first three reporting periods (cycles 1 to 6) is listed in Table 2. Hematologic toxicity predominated, with the majority of patients experiencing grade 3 or 4 thrombocytopenia and neutropenia after every cycle. Among the 30 patients who received the first two cycles of GV, two

Table 1. Clinical Characteristics of Eligible Patients Enrolled Onto AHOD0321 (N = 30)

Characteristic	No.	%
Age, years		
Median	17.7	
Range	10.7-29.4	
Sex		
Male	17	57
Female	13	43
Ann Arbor stage at initial diagnosis		
I	0	0
II	14	47
III	4	13
IV	12	40
Histologic subtype		
Nodular sclerosis	24	80
Lymphocyte predominant	2	7
Mixed cellularity	1	3
Unclear or missing	3	10
Time from initial diagnosis to enrollment on AHOD0321, months		
Median	17.6	
Range	6.2-86	
Patients with early relapse or primary refractory disease		
≤ 18 months from diagnosis to enrollment on AHOD0321	17	
Late relapse (> 18 months)	13	
Therapy prior to AHOD0321		
≥ 2 chemotherapy regimens	13	43
≥ 1 chemotherapy regimen plus autologous SCT	17	57
≥ 1 chemotherapy regimen plus allogeneic SCT	0	0
Prior exposure to gemcitabine or vinorelbine		
Gemcitabine	2	7
Cumulative prior gemcitabine, range (mg/m ²)	4,000-28,500	
Vinorelbine	13	43
Cumulative prior vinorelbine, mg/m ²		
Median	100	
Range	72-300	

Abbreviation: SCT, stem-cell transplantation.

patients experienced febrile neutropenia in the absence of a documented infection, and eight infections were documented either clinically or microbiologically in the setting of grade 3 to 4 neutropenia. The documented infections included the following: otitis externa, meningitis, gingivitis, sinusitis, cellulitis, urinary tract infection, catheter-related infection, and wound infection. In some cases, more than one infection was diagnosed in a single patient. Anemia and transient elevation in transaminases were the other toxicities that occurred in more than 10% of patients. There were no toxic deaths.

One patient developed weight gain and edema 2 weeks after her fourth cycle of GV and was found to have a pericardial effusion. Although her symptoms gradually improved, the effusion did not resolve, so the fluid was drained and a pericardial window was placed surgically. Analysis of the pericardial fluid revealed neither infection nor malignant cells. Her fifth cycle of GV was followed by reaccumulation of the pericardial effusion, along with bilateral pleural effusions. The patient had radiographic evidence of a CR, so was electively taken off treatment for unrelated donor stem-cell transplantation after the

effusions resolved. No further cycles of GV were given. Because this patient had received external-beam irradiation to the mediastinum before enrolling on AHOD0321, this complication was felt to be due to radiation recall.

One secondary malignancy has been documented among the patients treated on this protocol. A patient with delayed platelet recovery after a single cycle of GV was removed from study by his physician to seek alternative therapy. Two months later, this patient was diagnosed with myelodysplastic syndrome and treated with matched sibling stem-cell transplantation.

Disease Responses

Nineteen of 25 patients had measurable responses, for an observed response rate of 76% (95% exact binomial CI, 54.9% to 90.6%). Among the patients achieving some measurable response, best responses included six CRs (24%; three at cycle 2, two at cycle 4, and one at cycle 10), 11 VGPRs (44%; seven at cycle 2, three at cycle 4, and one at cycle 6), and two PRs (8%; one at cycle 2 and one at cycle 6). The six patients who did not achieve any response on protocol initially had SD; PD appeared between cycles 2 to 7. One more patient, who had achieved a CR after 10 cycles, experienced disease recurrence on study at cycle 15.

Patients who had undergone ASCT before GV tended to be more likely to respond to GV (six CRs, five VGPRs, and two PRs among 15 assessable patients) than those who had not undergone prior ASCT (six VGPRs among 10 assessable patients; $P = .18$, Fisher's exact test). There was also no significant difference in response rate between those patients who had prior exposure to vinorelbine (three CRs, five VGPRs, and one PR among 12 assessable patients) and those with no prior vinorelbine (three CRs, six VGPRs, and one PR among 13 assessable patients).

Among patients with primary refractory disease or early relapse (defined by an interval ≤ 18 months between initial diagnosis with HD and enrollment onto AHOD0321), there were eight responses (one PR, six VGPRs, and one CR) of 13 assessable patients (62%). The response rate was greater among patients with later relapses: 11 responses (one PR, five VGPRs, five CRs) of 12 assessable patients (92%). However, this difference was not statistically significant ($P = .17$; Fisher's exact test).

Responses increased among those who remained on treatment longer than two cycles. Only 13 (52%) of the 25 assessable patients had measurable responses after just the first two cycles. Of the 11 patients who had SD after two cycles and continued on therapy, six patients (55%) went on to have a measurable response, including four VGPRs, one PR, and one CR.

Survival Outcomes

Although the primary end point for this phase II study was response rate, event-free survival and overall survival were monitored. The estimated 1-year event-free and overall survival rates are 59.5% (95% CI, 39.8% to 74.6%) and 86.0% (95% CI, 66.8% to 94.5%), respectively (Fig 1). Median follow-up among the 22 patients who were last reported as being alive is 1.9 years (range, 0.6 to 2.6 years). Sixteen patients experienced at least one event; the reported first events were relapse/progression ($n = 12$), second malignancy (myelodysplastic syndrome; $n = 1$), and death ($n = 3$).

Table 2. Grade 3 to 4 Toxicity by Cycle

Grade 3 to 4 Toxicity	Cycles 1 and 2 (n = 30)		Cycles 3 and 4 (n = 21)		Cycles 5 and 6 (n = 8)	
	No.	%	No.	%	No.	%
Hematologic						
Hemoglobin	15	50.0	11	52.4	4	50.0
Leucocytes, total WBC	22	73.3	15	71.4	6	75.0
Neutrophils, ANC	23	76.7	15	71.4	6	75.0
Platelets	26	86.7	17	81.0	6	75.0
Gastrointestinal or metabolic						
Dehydration		0.0		0.0	1	12.5
Mucositis	1	3.3		0.0	1	12.5
Vomiting	1	3.3		0.0		0.0
Constipation		0.0		0.0		0.0
ALT	10	33.3	5	23.8	1	12.5
AST	5	16.7		0.0		0.0
Bilirubin	2	6.7		0.0	2	25.0
Glucose		0.0		0.0	1	12.5
Infectious						
Fever without neutropenia	1	3.3		0.0		0.0
Fever with neutropenia, no evident source	2	6.7	2	9.5	1	12.5
Infection in the setting of neutropenia	8	26.7	2	9.5	1	12.5
Other						
Hypertension		0.0		0.0		0.0
Hypotension		0.0		0.0	1	12.5
Pericardial effusion		0.0	1	4.8	1	12.5
Fatigue		0.0		0.0	1	12.5
Neuropathy, motor		0.0		0.0		0.0
Neuropathy, sensory		0.0		0.0		0.0
Pain, chest		0.0		0.0	1	12.5
Pain, limb	1	3.3		0.0		0.0
Pain, headache	1	3.3		0.0	1	12.5
Carbon monoxide diffusion capacity		0.0	1	4.8		0.0
Dyspnea		0.0		0.0	2	25.0
Hypoxia		0.0		0.0	1	12.5
Pleural effusion, nonmalignant		0.0		0.0	1	12.5
Pneumonitis/pulmonary infiltrates		0.0		0.0	1	12.5
Thrombosis/thrombus/embolism		0.0	1	4.8		0.0

NOTE. Toxicity was reported after every two cycles. The number of patients reporting grade 3 to 4 toxicity in each of the first three reporting periods is shown. Abbreviation: ANC, absolute neutrophil count.

DISCUSSION

GV has been used successfully in combination for patients with breast^{33,36} or non-small-cell lung cancer.^{27,50,51} However, there are limited published data regarding the use of this combination for patients with HD. Twenty of 29 adults with HD had disease stabilization or response after combination treatment with GV on trials at three institutions.⁵²⁻⁵⁴ After the Children's Oncology Group study described in this report opened, two pediatric patients treated with this combination were reported to have objective responses.⁵⁵

We now show that the response rate to GV among children and young adults with relapsed or refractory HD (76%; 95% CI, 54.9% to 90.6%) is greater than that reported for either drug alone. Because a substantial fraction of patients in this cohort did not experience their best radiographic response after only two cycles, all patients with less than a CR after two cycles should continue on for a minimum of two additional cycles.

It should be noted, however, that responses to GV on this protocol were assessed primarily by size reduction, as demonstrated by

computed tomography (CT). Response criteria for patients with HD were recently updated by an international working group,⁵⁶ taking into account the availability and the higher specificity of FDG-PET: patients whose tumors are FDG-PET positive before therapy will be designated as having a CR if their tumors are PET negative after treatment, regardless of the size of the residual mass on CT. As a result, it is likely that some patients treated with GV achieved a CR by these newer criteria earlier than we could verify by CT criteria.

Toxicity was tolerable and consisted primarily of reversible myelosuppression. Notably, there were no cases of noncardiogenic pulmonary edema, a rare complication of therapy with gemcitabine.^{57,58} However, a single patient developed an unexpected pericardial effusion, possibly as a result of radiation recall. Gemcitabine has been linked to radiation recall, affecting either skin⁵⁹ or internal organs.⁶⁰⁻⁶³ A small case series described pericardial effusions among adults with lymphoma treated with gemcitabine after mediastinal radiation.⁶⁴ Some of these patients were re-treated with gemcitabine, without recurrence of a pericardial effusion. We conclude that patients who have received prior mediastinal radiation can be safely

Fig 1. Event-free survival (EFS) and overall survival (OS) for patients enrolled onto AHOD0321. Survival was monitored from the time of enrollment. With median follow-up of 1.9 years, the estimated 1-year EFS and OS rates are 59.5% (95% CI, 39.8% to 74.6%) and 86.0% (95% CI, 66.8% to 94.5%), respectively.

treated with GV, but that a rapid evaluation should be done in any patient who develops new symptoms suggestive of pericardial or pleural effusion.

In conclusion, the response rate to GV observed among these heavily pretreated patients was greater than that reported for either

drug alone, with tolerable toxicity. On the basis of these results, further evaluation of GV for patients with HD seems warranted.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

Conception and design: Peter D. Cole, Cindy L. Schwartz, Richard A. Drachtman, Pedro A. de Alarcon, Tanya M. Trippett

Administrative support: Cindy L. Schwartz

Provision of study materials or patients: Peter D. Cole, Cindy L. Schwartz, Richard A. Drachtman

Collection and assembly of data: Peter D. Cole, Richard A. Drachtman, Lu Chen

Data analysis and interpretation: Peter D. Cole, Cindy L. Schwartz, Lu Chen, Tanya M. Trippett

Manuscript writing: Peter D. Cole, Cindy L. Schwartz, Richard A. Drachtman, Pedro A. de Alarcon, Lu Chen

Final approval of manuscript: Peter D. Cole, Cindy L. Schwartz, Richard A. Drachtman, Pedro A. de Alarcon, Lu Chen, Tanya M. Trippett

REFERENCES

- Lieskovsky YE, Donaldson SS, Torres MA, et al: High-dose therapy and autologous hematopoietic stem-cell transplantation for recurrent or refractory pediatric Hodgkin's disease: Results and prognostic indices. *J Clin Oncol* 22:4532-4540, 2004
- Lavoie JC, Connors JM, Phillips GL, et al: High-dose chemotherapy and autologous stem cell transplantation for primary refractory or relapsed Hodgkin lymphoma: Long-term outcome in the first 100 patients treated in Vancouver. *Blood* 106:1473-1478, 2005
- Josting A: Autologous transplantation in relapsed and refractory Hodgkin's disease. *Eur J Haematol Suppl* 141:145, 2005
- Hagemeister FB, Tannir N, McLaughlin P, et al: MIME chemotherapy (methyl-GAG, ifosfamide, methotrexate, etoposide) as treatment for recurrent Hodgkin's disease. *J Clin Oncol* 5:556-561, 1987
- Plunkett W, Huang P, Xu YZ, et al: Gemcitabine: Metabolism, mechanisms of action, and self-potentiation. *Semin Oncol* 22:3-10, 1995
- Santoro A, Bredenfeld H, Devizzi L, et al: Gemcitabine in the treatment of refractory Hodgkin's disease: Results of a multicenter phase II study. *J Clin Oncol* 18:2615-2619, 2000
- Zinzani PL, Bendandi M, Stefoni V, et al: Value of gemcitabine treatment in heavily pretreated Hodgkin's disease patients. *Haematologica* 85:926-929, 2000
- Toh HC, Sun L, Koh CH, et al: Vinorelbine induces apoptosis and caspase-3 (CPP32) expression in leukemia and lymphoma cells: A comparison with vincristine. *Leuk Lymphoma* 31:195-208, 1998
- Rule S, Tighe M, Davies S, et al: Vinorelbine in the treatment of lymphoma. *Hematol Oncol* 16:101-105, 1998
- Devizzi L, Santoro A, Bonfante V, et al: Vinorelbine: An active drug for the management of patients with heavily pretreated Hodgkin's disease. *Ann Oncol* 5:817-820, 1994
- Devizzi L, Santoro A, Bonfante V, et al: Vinorelbine: A new promising drug in Hodgkin's disease. *Leuk Lymphoma* 22:409-414, 1996
- Herbst RS, Lynch C, Vasconcelles M, et al: Gemcitabine and vinorelbine in patients with advanced lung cancer: Preclinical studies and report of a phase I trial. *Cancer Chemother Pharmacol* 48:151-159, 2001
- Bajetta E, Chiara Stani S, De Candis D, et al: Gemcitabine plus vinorelbine as first-line chemotherapy in advanced non-small cell lung carcinoma: A phase II trial. *Cancer* 89:763-768, 2000
- Beretta GD, Michetti G, Belometti MO, et al: Gemcitabine plus vinorelbine in elderly or unfit patients with non-small cell lung cancer. *Br J Cancer* 83:573-576, 2000
- Camps C, Martinez EN, Jaime AB: Second-line treatment with gemcitabine and vinorelbine in non-small-cell lung cancer (NSCLC) cisplatin failures: A pilot study. *Lung Cancer* 27:47-53, 2000
- Chen YM, Perng RP, Yang KY, et al: 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, 2000
- Esteban E, Fra J, Corral N, et al: Phase I/II study of gemcitabine plus vinorelbine in non-small cell lung cancer. *Invest New Drugs* 20:73-82, 2002
- Feliu J, Lopez Gomez L, Madronal C, et al: Gemcitabine plus vinorelbine in non-small cell lung carcinoma patients age 70 years or older or patients who cannot receive cisplatin: Oncopaz Cooperative Group. *Cancer* 86:1463-1469, 1999
- Frasci G, Lorusso V, Panza N, et al: Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. *J Clin Oncol* 18:2529-2536, 2000
- Gridelli C, Cigolari S, Gallo C, et al: Activity and toxicity of gemcitabine and gemcitabine + vinorelbine in advanced non—small-cell lung cancer elderly patients: Phase II data from the Multicenter Italian Lung Cancer in the Elderly Study (MILES) randomized trial. *Lung Cancer* 31:277-284, 2001
- Gridelli C, Frontini L, Perrone F, et al: 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, 2000
- Hirsh V, Langleben A, Ayoub J, et al: Flexible chemotherapy regimen with gemcitabine and vinorelbine for metastatic non-small cell lung carcinoma: A phase II multicenter trial. *Cancer* 92:830-835, 2001
- Herbst RS, Khuri FR, Lu C, et al: The novel and effective nonplatinum, nontaxane combination of gemcitabine and vinorelbine in advanced non-small cell lung carcinoma: Potential for decreased toxicity and combination with biological therapy. *Cancer* 95:340-353, 2002
- Kawasaki Y, Kato K, Kobayashi K, et al: Successful outpatient treatment with chemotherapy of weekly gemcitabine and vinorelbine for a patient with recurrent lung cancer. *Gan to Kagaku Ryoho* 29:107-109, 2002
- Kawasaki Y, Koshohbu T, Nakatani S, et al: Successful treatment with chemotherapy of vinorelbine and gemcitabine for an elderly patient with advanced non-small cell lung cancer. *Gan to Kagaku Ryoho* 30:515-517, 2003
- Krajnik G, Mohn-Staudner A, Thaler J, et al: 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, 2000
- Laack E, Mende T, Benk J, et al: Gemcitabine and vinorelbine as first-line chemotherapy for advanced non-small cell lung cancer: A phase II trial. *Eur J Cancer* 37:583-590, 2001
- Lilenbaum R: Options in advanced non-small cell lung cancer: A review and report on a phase II

study of vinorelbine plus gemcitabine. *Oncologist* 6:16-19, 2001

29. Lilenbaum R, Cano R, Schwartz M, et al: Gemcitabine and vinorelbine in advanced nonsmall cell lung carcinoma: A phase II study. *Cancer* 88: 557-562, 2000
30. Lorusso V, Crucitta E, Panza N, et al: Phase I/II study of paclitaxel, gemcitabine and vinorelbine as first-line chemotherapy of non-small-cell lung cancer. *Ann Oncol* 13:1862-1867, 2002
31. Hortobagyi GN: Treatment of advanced breast cancer with gemcitabine and vinorelbine. *Oncology (Huntington)* 15:15-17, 2001
32. Hortobagyi GN: Gemcitabine in combination with vinorelbine for treatment of advanced breast cancer. *Clin Breast Cancer* 3:34-38, 2002
33. Lobo F, Virizuela JA, Dorta FJ, et al: Gemcitabine/vinorelbine in metastatic breast cancer patients previously treated with anthracyclines: Results of a phase II trial. *Clin Breast Cancer* 4:46-50, 2003
34. Nicolaides C, Dimopoulos MA, Samantas E, et al: Gemcitabine and vinorelbine as second-line treatment in patients with metastatic breast cancer progressing after first-line taxane-based chemotherapy: A phase II study conducted by the Hellenic Cooperative Oncology Group. *Ann Oncol* 11:873-875, 2000
35. Sanal SM, Gokmen E, Karabulut B, et al: Gemcitabine and vinorelbine combination in patients with metastatic breast cancer. *Breast J* 8:171-176, 2002
36. Stathopoulos GP, Rigatos SK, Pergantas N, et al: Phase II trial of biweekly administration of vinorelbine and gemcitabine in pretreated advanced breast cancer. *J Clin Oncol* 20:37-41, 2002
37. Valenza R, Leonardi V, Gebbia V, et al: Gemcitabine and vinorelbine in pretreated advanced breast cancer: A pilot study. *Ann Oncol* 11:495-496, 2000
38. Grunewald R, Kantarjian H, Du M, et al: Gemcitabine in leukemia: A phase I clinical, plasma, and cellular pharmacology study. *J Clin Oncol* 10:406-413, 1992
39. Grunewald R, Abbruzzese JL, Tarasoff P, et al: Saturation of 2',2'-difluorodeoxycytidine 5'-triphosphate accumulation by mononuclear cells during a phase I trial of gemcitabine. *Cancer Chemother Pharmacol* 27:258-262, 1991
40. Abbruzzese J, Grunewald R, Weeks E, et al: A phase I clinical, plasma, and cellular pharmacology study of gemcitabine. *J Clin Oncol* 9:491-498, 1991
41. Touroutoglou N, Gravel D, Raber MN, et al: Clinical results of a pharmacodynamically-based strategy for higher dosing of gemcitabine in patients with solid tumors. *Ann Oncol* 9:1003-1008, 1998
42. Patel SR, Gandhi V, Jenkins J, et al: Phase II clinical investigation of gemcitabine in advanced soft tissue sarcomas and window evaluation of dose rate on gemcitabine triphosphate accumulation. *J Clin Oncol* 19:3483-3489, 2001
43. Sezer O, Eucker J, Jakob C, et al: Achievement of complete remission in refractory Hodgkin's disease with prolonged infusion of gemcitabine. *Invest New Drugs* 19:101-104, 2001
44. Akrivakis K, Schmid P, Flath B, et al: Prolonged infusion of gemcitabine in stage IV breast cancer: A phase I study. *Anticancer Drugs* 10:525-531, 1999
45. Schmid P, Akrivakis K, Flath B, et al: Phase II trial of gemcitabine as prolonged infusion in metastatic breast cancer. *Anticancer Drugs* 10:625-631, 1999
46. Pollera CF, Ceribelli A, Crecco M, et al: Prolonged infusion gemcitabine: A clinical phase I study at low- (300 mg/m²) and high-dose (875 mg/m²) levels. *Invest New Drugs* 15:115-121, 1997
47. Tempero M, Plunkett W, Ruiz van Haperen V, et al: Randomized phase II trial of dose intense gemcitabine by standard infusion vs. fixed dose rate in metastatic pancreatic adenocarcinoma. *Proc Am Soc Clin Oncol* 18:273a, 1999 (abstr 1048)
48. Lister TA, Crowther D, Sutcliffe SB, et al: Report of a committee convened to discuss the evaluation and staging of patients with Hodgkin's disease: Cotswolds meeting. *J Clin Oncol* 7:1630-1636, 1989 [Erratum: *J Clin Oncol* 8:1602, 1990]
49. Therasse P, Arbuck SG, Eisenhauer EA, et al: New guidelines to evaluate the response to treatment in solid tumors: European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst* 92:205-216, 2000
50. Laack E, Dickgreber N, Muller T, et al: Randomized phase III study of gemcitabine and vinorelbine versus gemcitabine, vinorelbine, and cisplatin in the treatment of advanced non-small-cell lung cancer: From the German and Swiss Lung Cancer Study Group. *J Clin Oncol* 22:2348-2356, 2004
51. Lorusso V, Carpagnano F, Frasci G, et al: Phase I/II study of gemcitabine plus vinorelbine as first-line chemotherapy of non-small-cell lung cancer. *J Clin Oncol* 18:405-411, 2000
52. Spencer A, Arthur C, Schwarzer AP: Vinorelbine and gemcitabine with filgrastim (VGF) support shows significant activity against advanced lymphoma. *Proc Am Soc Hematol* 100:781a, 2002 (abstr 3088)
53. Hamlin PA, Kewalramani T, Schaindlin P, et al: Gemcitabine/vinorelbine: A well tolerated and effective regimen for patients with relapsed/refractory Hodgkin's disease (HD) who fail autologous stem cell transplantation (ASCT). *Proc Am Soc Hematol* 100:634a, 2002 (abstr 2498)
54. Spencer A, Reed K, Arthur C: Pilot study of an outpatient-based approach for advanced lymphoma using vinorelbine, gemcitabine and filgrastim. *Intern Med J* 37:760-766, 2007
55. Ozkaynak MF, Jayabose S: Gemcitabine and vinorelbine as a salvage regimen for relapse in Hodgkin lymphoma after autologous hematopoietic stem cell transplantation. *Pediatr Hematol Oncol* 21:107-113, 2004
56. Cheson BD, Pfistner B, Juweid ME, et al: Revised response criteria for malignant lymphoma. *J Clin Oncol* 25:579-586, 2007
57. Aapro MS, Martin C, Hatty S: Gemcitabine: A safety review. *Anticancer Drugs* 9:191-201, 1998
58. Briassoulis E, Pavlidis N: Noncardiogenic pulmonary edema: An unusual and serious complication of anticancer therapy. *Oncologist* 6:153-161, 2001
59. Schwartz BM, Khuntia D, Kennedy AW, et al: Gemcitabine-induced radiation recall dermatitis following whole pelvic radiation therapy. *Gynecol Oncol* 91:421-422, 2003
60. Friedlander PA, Bansal R, Schwartz L, et al: Gemcitabine-related radiation recall preferentially involves internal tissue and organs. *Cancer* 100:1793-1799, 2004
61. Fakih MG: Gemcitabine-induced rectus abdominus radiation recall. *JOP* 7:306-310, 2006
62. Saif MW, Sellers S, Russo S: Gemcitabine-related radiation recall in a patient with pancreatic cancer. *Anticancer Drugs* 17:107-111, 2006
63. Schwarte S, Wagner K, Karstens JH, et al: Radiation recall pneumonitis induced by gemcitabine. *Strahlenther Onkol* 183:215-217, 2007
64. Vogl DT, Glatstein E, Carver JR, et al: Gemcitabine-induced pericardial effusion and tamponade after unblocked cardiac irradiation. *Leuk Lymphoma* 46:1313-1320, 2005