Cancer Chemother Pharmacol (2007) 59:269–274
DOI 10.1007/s00280-006-0266-x

ORIGINAL ARTICLE

Phase II study of a gemcitabine and cisplatin combination regimen in taxane resistant metastatic breast cancer

Jae Hong Seo · Sang Cheul Oh · Cheul Won Choi · Byung Soo Kim · Sang Won Shin · Yeul Hong Kim · Jun Suk Kim · Ae-Ree Kim · Jae-Bok Lee · Bum Hwan Koo

Received: 16 February 2006 / Accepted: 9 May 2006 / Published online: 9 June 2006

Abstract *Purpose*: To determine the safety and efficacy of gemcitabine and cisplatin in patients with taxane resistant metastatic breast cancer. *Patients and methods*: Thirty-three taxane resistant metastatic breast cancer patients were treated with gemcitabine 1,250 mg/m^2 IV infusion over 30 min on days 1 and 8, and with cisplatin 75 mg/m^2 by IV infusion over 1 h on day 1 in 21 day cycles. *Results:* Of the 30 evaluable patients, there were 9 (30%) partial responses and no complete response, an overall objective response rate of 30%. Median time to progression and median survival duration for all study subjects were 7 (95% CI 5.1–8.9 months) and 15 months (95% CI 10.5–19.5 months), respectively. Toxicities included grade 3 and 4 leucopenia in 10 (30%), thrombocytopenia in 6 (18%), anemia in 2 (6%) and oral mucositis in 2 (6%). No grade 3 or 4 peripheral neuropathy, renal dysfunction, hepatic dysfunction, or nausea/vomiting was observed, and no treatment-related deaths occurred. *Conclusion:* The described gemcitabine plus cisplatin combination was found to be an active and tolerable salvage regimen in patients with taxane resistant metastatic breast cancer.

Keywords Gemcitabine · Cisplatin · Taxane resistant · Metastatic breast cancer

J. H. Seo · S. C. Oh · C. W. Choi · B. S. Kim · S. W. Shin · Y. H. Kim · J. S. Kim (✉)
Department of Internal Medicine,
Division of Hematology/Oncology, College of Medicine,
Korea University Guro Hospital, 97 Gurodong-gil, Guro-ku,
Seoul 152-703, Korea
e-mail: kjs6651@ns.kumc.or.kr

A. R. Kim
Department of Pathology, College of Medicine,
Korea University, Seoul, Korea

J. B. Lee · B. H. Koo
Department of Surgery, College of Medicine,
Korea University, Seoul, Korea

Introduction

Although present metastatic breast cancer treatments cannot cure, they can improve quality of life (QOL) and may increase life span [1]. Therefore, treatment related toxicities must be balanced against QOL and life span gains when selecting treatment modalities. From the viewpoint of chemotherapy, various treatment options are available involving active single agents and their combinations. Anthracyclines and taxanes are the most active breast cancer chemotherapeutic agents known at present, and therefore, the great majority of patients are treated with both drugs initially in an adjuvant setting or as a primary therapy in a metastatic setting. However, recently, many other drugs have been developed for use in breast cancer patients, i.e., gemcitabine, vinorelbine and pegylated liposomal doxorubicin. However, no single drug has achieved a meaningful response rate without cross-resistance to taxane, and because of these limitations, no standard chemotherapy regimen has been established for the treatment of patients with taxane resistant metastatic breast cancer, and thus, the identification of active salvage agents is urgently required. Currently, palliation remains the main goal of management in taxane resistant metastatic breast cancer.

Gemcitabine is a recently introduced nucleoside antimetabolite of deoxycytidine. It has a novel mode of action and is active against a wide range of solid tumors [2]. Moreover, gemcitabine possesses a favorable toxicity profile, with mild myelosuppression and minimal nonhematologic toxicity, and has been tested in metastatic breast cancer as a single agent and as a component in combination chemotherapy [3–5]. Moreover, its objective single agent response rates in non-small cell lung and breast cancers range from 14 to 46%, depending on the dose administered and whether patients have received prior chemotherapy or not.

On the other hand, cisplatin is a bifunctional DNA cross-linking agent with marked activity against various solid tumors. However, cisplatin has not been established as a breast cancer therapeutic. In fact, only three studies have examined cisplatin as a single agent in previously untreated metastatic breast cancer [6–8]. However, when it was evaluated as a single agent in pretreated metastatic breast cancer patients, the observed response rate was limited [9–14]. Nevertheless, the gemcitabine and cisplatin combination has been shown to be synergistic in vitro and additive in vivo in ovarian, colon, and in head and neck squamous carcinoma cell lines [15–17]. In a phase II study of 30 patients with relapsed metastatic breast cancer, a 50% response rate was observed when gemcitabine and cisplatin were administered using a 28-day cycle [18]. Furthermore, a response rate of 40% was observed in anthracycline- and taxane-pretreated metastatic breast cancer patients [19]. In addition, gemcitabine and cisplatin combination chemotherapy when used as a first-line treatment in metastatic breast cancer patients produced an overall response rate of 54.5% with a CR rate of 13.6% [20].

Thus, the present study was conducted to verify the clinical efficacy and safety of gemcitabine and cisplatin combination salvage therapy in taxane resistant metastatic breast cancer patients.

Materials and methods

Eligibility criteria

Thirty-three patients with histologically confirmed metastatic breast cancer, who either progressed during therapy or progressed within 6 months of initiating a taxane-containing chemotherapy, were enrolled in this study, which was approved by institutional review boards. All patients provided written informed consent.

Other inclusion criteria were as follows; (1) an age of 18–65 years; (2) an ECOG performance status of 0–2; (3) a life expectancy of more than 3 months; (4) a bidimensionally measurable metastatic lesion; (5) no central nervous system involvement or carcinomatous meningitis; (6) no active infection; (7) no history of a prior malignancy or significant medical disease; (8) no previous history of gemcitabine and/or cisplatin treatment; (9) a normal hematologic function (neutrophil count $>2.0\times10^9$/l, platelets $>150\times10^9$/l, hemoglobin >10 g/dl); (10) adequate renal and hepatic functions (serum total bilirubin, ALT, and AST levels of <twice the normal upper limit, serum creatinine level <1.5 mg/dl); and (11) a normal heart function with a left ventricular ejection fraction of >60%. Prior radiation treatment completed at least 4 weeks prior to the study registration date was permitted, if it encompassed <30% of the total marrow-bearing skeleton. Hormonal therapies were discontinued at least 3 weeks before study entry. Taxane resistance was classified as primary resistance if the disease progressed during chemotherapy without response or stabilization, or as secondary resistance if the disease progressed within 6 months of achieving complete response, partial response, or stabilization after a taxane containing chemotherapy.

Treatment plan

Cycles of gemcitabine (1,250 mg/m^2 by intravenous infusion over 30 min on days 1 and 8) and cisplatin (75 mg/m^2 by intravenous infusion over 1 h on day 1) chemotherapy were administered every 21 days. Cisplatin treatment was administered with pre-hydration and post-hydration measures. Chemotherapy was administered for a maximum of eight cycles and was discontinued in the event of; unacceptable toxicity, a treatment delay of longer than 2 weeks, disease progression, or patient refusal.

Moderate antiemetic drugs, such as, methoclopromide were administered from day 1 to day 3, but prophylactic hematopoietic growth factors were not routinely administered. In addition, from the day that a patient's neutrophil count dropped below 1×10^9/l after chemotherapy until the day that the neutrophil count recovered to more than 1.5×10^9/l, GM-CSF (Leucogen, Lucky-Gumsung Co., Korea) 400 μg/s.c was injected daily. Subsequent chemotherapy cycles were started on day 22 for patients whose neutrophil counts exceeded 1.5×10^9/l and whose platelet counts exceeded 100×10^9/l. If these values were not reached by the date of the scheduled retreatment, therapy was delayed in weekly intervals, and if these hematological criteria were not fulfilled after a delay of 2 weeks, the patient concerned was removed from the study. Doses of gemcitabine and cisplatin were reduced by 25%

during subsequent cycles if neutrophil and platelet count nadirs were $<0.5\times10^9$/l or $<50\times10^9$/l, respectively, or if neutropenic fever developed. In addition, on chemotherapy day 8, CBC was performed before gemcitabine treatment. Gemcitabine was omitted in cases of grade 4 hematologic toxicity on day 8. A maximum of 6 cycles were administered, but if a patient wanted further treatment and belonged to the responder group after 6 cycles of chemotherapy, a further two cycles were permitted. The primary endpoint of this study was time to progression (TTP) and secondary endpoints included tumor response rate, overall survival and toxicities.

Pretreatment and follow-up studies

Before study enrollment, all patients underwent a complete history taking, a laboratory evaluation, and physical examination. The laboratory evaluation included complete blood cell (CBC) and differential counts, biochemical profile, carcinoembryonic antigen (CEA), CA 15-3, LDH, urinalysis, baseline ECG, chest X-ray, ultrasonographic or CT scan of the abdomen and any suspicious areas, and a bone scan. Physical examination, ECOG performance status (PS), CBC, and differential counts, biochemical profile, significant tumor markers, and chest X-rays were re-evaluated before the start of each cycle. Tumor measurements were documented at the end of every second cycle until the completion of treatment.

Response and toxicity evaluations

Treatment response was evaluated by two observers not less than four weeks apart. Complete response (CR) was defined as the disappearance of all clinical evidence of active tumor and the absence of disease-related symptoms for a minimum of 4 weeks. Partial response (PR) was defined as a $\geq$50% reduction in the sum of the products of the biperpendicular diameters of all measurable lesions, without the appearance of a new lesion for at least 4 weeks. When multiple metastasis sites were present, the largest masses were considered as index lesions. Stable disease (SD) was defined as no change in tumor size or a <25% increase or a <25% decrease over the previous 4 weeks at least. Progressive disease (PD) was defined as an increase of $\geq$25% in the size of at least one measurable lesion, or the appearance of a new lesion involving pleural effusion or ascites substantiated by a positive cytology.

All patients that received one course of gemcitabine and cisplatin or more were evaluated for toxicities as required by intent-to-treat analysis. The types and severities of these toxicities were determined using World Health Organization (WHO) common toxicity scale criteria.

Statistical analysis

Response durations and survival determinations were measured from the gemcitabine and cisplatin chemotherapy start date. Time to progression was defined as the time from registration to the date of progression. Ninety-five percent response rate confidence intervals were calculated using the binomial theorem using Epi Info 6 (version 6.04b January 1997, Center for Disease Control). Survival and response durations were calculated using the Kaplan–Meier method in SPSS Ver. 10.0.7 of Windows (SPSS Inc. 1 Jun 2000 Chicago). P values of $\leq$0.05 were considered to indicate statistical significance.

Results

Patient characteristics

From January 2003 to June 2005, 33 patients were enrolled in this study. Of these, 3 patients were excluded from the response evaluation because they refused further treatment after only one cycle of chemotherapy. However, these 3 were included in the toxicity evaluations and in the survival analysis as is required by intent-to-treat analysis. Therefore, 30 patients were eligible for response evaluation. Median patient age was 56 years (range 35–68) and the majority of patients had an ECOG performance status of 0–1 (29, 88%). All patients had received a taxane-containing chemotherapy regimen in a metastatic setting before enrollment in the present study. Twenty-four patients who had relapsed during follow-up after adjuvant therapy received a taxane-containing regimen, and 9 patients received a taxane-containing regimen in a metastatic setting initially. Of the 33 patients, 10 (30%) were primary taxane resistant, and 23 (70%) were secondary taxane resistant. Sites of metastasis, estrogen receptor statuses, menopause statuses, numbers of previous chemotherapies, intentions of prior taxane therapies, prior anthracycline and hormonal therapy, and details of adjuvant radiation therapies are listed in Table 1.

Drug delivery

After the first cycle of chemotherapy, the initial planned dose of gemcitabine (1,250 mg/m^2) and cisplatin (75 mg/m^2) proved unfeasible in 5 patients

Table 1 Characteristics of the enrolled patients

Characteristics	No. of patients (%)
Performance status	
0	8/33 (24)
1	21/33 (64)
2	4/33 (12)
Predominant site of metastasis	
Lung	27/33 (82)
Bone	19/33 (58)
Liver	10/33 (30)
Skin/soft tissue	4/33 (12)
Lymph nodes	5/33 (15)
Estrogen receptor status	
Positive	18/33 (55)
Negative	15/33 (45)
Menstrual status	
Premenopausal	8/33 (24)
Postmenopausal	25/33 (76)
Numbers of previous chemotherapy (contain adjuvant chemotherapy)	
1	9/33 (27)
2	24/33 (73)
Taxane resistance	
Primary	10/33 (30)
Secondary	23/33 (70)
Intention of hormonal therapy	
Adjuvant	14/33 (42)
Palliative	1/33 (3)
Adjuvant radiation therapy	
Yes	20/33 (61)
No	13/33 (39)

because of grade 4 leucopenia (n=2), grade 4 thrombocytopenia (n=1), and grade 3 leucopenia with neutropenic fever (n=2). Thus, as mentioned above, these patients were subsequently treated using a 25% dose reduction. A total of 138 cycles were administered to the 33 patients with a median number of four cycles per patient (range 1–8). Median relative dose-intensities were 93% for gemcitabine (range, 71–100%) and 96% for cisplatin (range, 79–100%).

Efficacy

Thirty patients were assessed for response evaluation. Of these 30 anthracycline- and taxane-pretreated cases, 9 achieved a partial response, and 13 had stable disease giving an objective response rate of 30% (95% CI, 15.4–49.6%) (Table 2). Median time to progression was 7 months (95% CI, 5.1–8.9 months) and median survival duration was 15 months (95% CI, 10.5–19.5 months).

Toxicities

Toxicities were evaluated over 138 chemotherapy cycles. Total reversible alopecia occurred in all 33 cases, and reversible grade 3 and 4 leucopenia occurred in 8 and 2 patients, respectively. Patients with grade 3 and 4 leucopenia were treated using intravenous GM-CSF 400 μg/s.c until full hematologic recovery. Two patients suffered from neutropenic fever during chemotherapy and were admitted and treated using empirical antibiotics and they were completely recovered without complication within a week. The other significant (grade 3 and 4) toxicities encountered were anemia (n=1), thrombocytopenia (n=6), and oral mucositis (n=2), and these all recovered completely without complication. However, other significant toxicities, such as, diarrhea, hypersensitivity reactions, peripheral neuropathy, hepatic dysfunction, and renal dysfunction were not observed. No chemotherapy-related deaths occurred; details of toxicities are documented in Table 3.

Table 2 Response to treatment by WHO criteria (evaluable patients no.=30) and progression free survival (median)

Efficacy variables	No.of months (% 95% confidence interval)
Complete response	0/30 (0%)
Partial response	9/30 (30%: 95% CI, 15.4–49.6)
Stable disease	13/30 (43%: 95% CI, 26.0–62.3)
Progressive disease	8/30 (27%: 95% CI, 13.0–46.2)
Progression free survival median (PFS median)	7 months (5.1–8.9 months)

Discussion

The increasing use of taxanes in adjuvant and first-line metastatic settings has created a need for effective therapeutic agents that prevent disease progression in this patient population. The commonly used agents include; capecitabine, vinorelbine, gemcitabine, pegylated liposomal doxorubicin, and irinotecan [21, 22]. However, few documented comparative randomized

Table 3 Major toxicities in 33 patients treated with gemcitabine and cisplatin

WHO grade	No. of patients (%)			
	0–1	2	3	4
Leukopenia	5 (15)	18 (55)	8 (24)	2 (6)
Thrombocytopenia	7 (21)	20 (61)	5 (15)	1 (3)
anemia	13 (39)	19 (58)	1 (3)	0 (0)
Peripheral neuropathy	25 (76)	8 (24)	0 (0)	0 (0)
Stomatitis/mucositis	17 (52)	14 (42)	2 (6)	0 (0)
Renal dysfunction	32 (97)	1 (3)	0 (0)	0 (0)
Nausea/vomiting	17 (52)	16 (48%)	0 (0)	0 (0)

Table 4 Phase II trials involving gemcitabine-containing combination regimens in anthracycline- and taxane-pretreated MBC

Study	Patients number	Regimen	Response rate (%)	Median time to progression (month)
Heinemann et al. [19]	38	Gemcitabine/cisplatin	40	6
Nagourney et al. [18]	30	Gemcitabine/cisplatin	50	5.9
Schmid et al. [24]	26	Gemcitabine/vinorelbine	30.4	4.6
Smorenburg et al. [25]	23	Weekly gemcitabine	0	1.9
Frasci et al. [23]	46	Gemcitabine/4-FU/folinic acid	37	6

trials have examined the relative efficacies of these agents in patients with diseases that could be considered taxane resistant. The majority of reports concern simple phase II trials of combinations of various candidate drugs. Table 4 summarizes a number of the phase II reports on gemcitabine-containing combination regimens in anthracycline- and taxane-pretreated metastatic breast cancer patients [18, 19, 23–25]. However, no gemcitabine-containing combinatorial regimes have been reported in taxane resistant metastatic breast cancer, and thus, no standard chemotherapy is available for taxane resistant metastatic breast cancer patients.

Anthracyclines are generally eliminated from consideration in a metastatic setting, because of the risk of anthracycline-induced cardiotoxicity, which is associated with a high cumulative anthracycline dose and an advanced age [26]. Thus, efficacious well-tolerated agents are urgently needed for use in this setting.

Clinically, a suitable gemcitabine and cisplatin combination regimen should meet the three criteria required of a salvage regimen, namely, pre-clinical evidence of synergy, absence of cross-resistance between components, and non-overlapping toxicity profiles [17]. Phase III trials studies have shown that gemcitabine and cisplatin can be used successfully to treat non-small cell lung and bladder cancer [27, 28], and thus, we decided to investigate the merits of this combination in anthracycline- and taxane-pretreated metastatic breast cancer patients.

All 33 patients with taxane resistance enrolled were treated with gemcitabine and cisplatin combination chemotherapy. The gemcitabine and cisplatin regimen used achieved partial response in 9 (30%) patients and stable disease in 13 (43%), and objective response rate of 30% (95% CI, 15.4–49.6%). These findings demonstrate that the gemcitabine and cisplatin regimen used is a clinically significant salvage regimen. However, the objective response rate observed during the present is lower than those reported previously [18, 19], which we attribute to the taxane resistance shown by our study subjects. Nevertheless, our patients showed a median survival duration of 15 months (95% CI, 10.5–19.5 months) and a median time to progression of 7 months (95% CI, 5.1–8.9 months). Moreover, the administered gemcitabine and cisplatin combination was well tolerated and no toxicity-related mortality occurred. Although the initial planned dose of gemcitabine 1,250 mg/m^2 and cisplatin 75 mg/m^2 proved unfeasible in 5 patients, because of grade 4 leucopenia (n=2), grade 4 thrombocytopenia (n=1), and grade 3 leucopenia with neutropenic fever (n=2), median study relative dose-intensities were 93% for gemcitabine (range, 71–100%) and 96% for cisplatin (range 79–100%).

In conclusion, the present study shows that the described gemcitabine and cisplatin combination is a relatively active salvage regimen with manageable toxicities in taxane resistant metastatic breast cancer patients. Therefore, we advocate that further well designed comparative studies should be conducted in a larger cohort to confirm our results and to verify the clinical feasibility of this regimen as a salvage treatment in taxane resistant metastatic breast cancer.

Acknowledgment This work was supported in part by the Brain Korea 21 Project and was supported by the Korean Health 21 R and D Project, Ministry of Health and Welfare, Republic of Korea (Grant no. 01-PG3-PG6-01GN07-0004).

References

1. Greenberg PA, Hortobagyi GN, Smith TL, Ziegler LD, Frye DK, Buzdar AU (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 14:2197–2205
2. Merriman RL, Hertel LW, Schultz RM, Houghton PJ, Houghton JA, Rutherford PG, et al (1996) Comparison of the antitumor activity of gemcitabine and ara-C in a panel of human breast, colon, lung and pancreatic xenograft models. Invest New Drugs 14:243–247
3. Abratt RP, Bezwoda WR, Falkson G, Goedhals L, Hacking D, Rugg TA (1994) Efficacy and safety profile of gemcitabine in non-small-cell lung cancer: a phase II study. J Clin Oncol 12:1535–1540
4. Gatzemeier U, Shepherd FA, Le Chevalier T, Weynants P, Cottier B, Groen HJ, et al (1996) Activity of gemcitabine in patients with non-small cell lung cancer: a multicentre, extended phase II study. Eur J Cancer 32:243–248

5. Seidman AD (2001) The evolving role of gemcitabine in the management of breast cancer. Oncology 60:189–198
6. Kolaric K, Roth A (1983) Phase II clinical trial of cis-dichlorodiammine platinum (cis-DDP) for antitumorigenic activity in previously untreated patients with metastatic breast cancer. Cancer Chemother Pharmacol 11:108–112
7. Mechl Z, Sopkova B (1984) CAP (cyclophosphamide, adriamycin, cisplatin in the treatment of advanced breast cancer. Neoplasma 31:431–435
8. Sledge GW Jr, Loehrer PJ Sr, Roth BJ, Einhorn LH (1988) Cisplatin as first-line therapy for metastatic breast cancer. J Clin Oncol 6:1811–1814
9. Bajorin D, Bosl GJ, Fein R (1987) Phase I trial of escalating doses of cisplatin in hypertonic saline. J Clin Oncol 5:1589–1593
10. Forastiere AA, Hakes TB, Wittes JT, Wittes RE (1982) Cisplatin in the treatment of metastatic breast carcinoma: A prospective randomized trial of two dosage schedules. Am J Clin Oncol 5:243–247
11. Martino S, Samal BA, Singhakowinta A, Yoshida S, Mackenzie M, Jain J et al (1984) A phase II study of cis-diamminedichloroplatinum II for advanced breast cancer. Two dose schedules. J Cancer Res Clin Oncol 108:354–356
12. Ostrow S, Egorin M, Aisner J, Bachur N, Wiernik PH (1980) High-dose cis-diamminedichloro-platinum therapy in patients with advanced breast cancer: pharmacokinetics, toxicity, and therapeutic efficacy. Cancer Clin Trials 3:23–27
13. Ramnath N, LoRusso P, Simon M, Martino S (1997) Phase II evaluation of cisplatin and WR2721 for refractory metastatic breast cancer. Am J Clin Oncol 20:368–372
14. Yap HY, Salem P, Hortobagyi GN, Bodey GP Sr, Buzdar AU, Tashima CK et al (1978) Phase II study of cis-dichlorodiammineplatinum(II) in advanced breast cancer. Cancer Treat Rep 62:405–408
15. Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ (1994) Synergistic interaction between cisplatin and gemcitabine in ovarian and colon cancer cell lines. Adv Exp Med Biol 370:139–143
16. Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Peters GJ (1996) Synergistic interaction between cisplatin and gemcitabine in vitro. Clin Cancer Res 2:521–530
17. Peters GJ, Bergman AM, Ruiz van Haperen VW, Veerman G, Kuiper CM, Braakhuis BJ (1995) Interaction between cisplatin and gemcitabine in vitro and in vivo. Semin Oncol 22:72–79
18. Nagourney RA, Link JS, Blitzer JB, Forsthoff C, Evans SS (2000) Gemcitabine plus cisplatin repeating doublet therapy in previously treated, relapsed breast cancer patients. J Clin Oncol 18:2245–2249
19. Heinemann V, Stemmler HJ, Wohlrab A, Bosse D, Losem C, Kahlert S, et al (2005) High efficacy of gemcitabine and cisplatin in patients with predominantly anthracycline- and taxane-pretreated metastatic breast cancer. Cancer chemother Pharmacol 15:1–7
20. Mohran TZ (2004) Gemcitabine and Cisplatin combination chemotherapy as a first-line treatment in patients with metastatic breast cancer. J Egypt Natl Canc Inst 16:8–14
21. Verma S, Trudeau M, Dranitsaris G, Clemons M, Joy AA, MacKey JR (2005) What is the best chemotherapy treatment option for anthracycline and taxane pretreated metastatic breast cancer? J Clin Oncol 23:6260
22. Keller AM, Mennel RG, Georgoulias VA, Nabholtz JM, Erazo A, Lluch A, et al (2004) Randomized phase III trial of pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastine in women with taxane-refractory advanced breast cancer. J Clin Oncol 22:3893–3901
23. Frasci G, D'Aiuto G, Comella P, Thomas R, Capasso I, Botti G, et al (2001) Gemcitabine/cyclophosphamide/5-fluorouracil/folinic acid triplet combination in anthracycline- and taxane-refractory breast cancer patients: a southern Italy cooperative oncology group phase I/II study. Semin Oncol 28:50–56
24. Schmid P, Heilmann V, Schulz CO, Dieing A, Lehenbauer-Dehm S, Jehn C et al (2005) Gemcitabine as prolonged infusion and vinorelbine in anthracycline and/or taxane pretreated metastatic breast cancer: a phase II study. J Cancer Res Clin Oncol 131:568–574
25. Smorenburg CH, Bontenbal M, Seynaeve C, van Zuylen C, de Heus G, Verweij J et al (2001) Phase II study of weekly gemcitabine in patients with metastatic breast cancer relapsing or failing both an anthracycline and a taxane. Breast Cancer Res Treat 66:83–87
26. Singal PK, Iliskovic N (1998) Doxorubicin-induced cardiomyopathy. N Engl J Med 339:900–905
27. Sandler AB, Nemunaitis J, Denham C, von Pawel J, Cormier Y, Gatzemeier U, et al (2000) Phase III trial of gemcitabine plus cisplatin versus cisplatin alone in patients with locally advanced or metastatic non-small-cell lung cancer. J Clin Oncol 18:122–130
28. von der Maase H, Hansen SW, Roberts JT, Dogliotti L, Oliver T, Moore MJ et al (2000) Gemcitabine and cisplatin versus methotrexate, vinblastine, doxorubicin, and cisplatin in advanced or metastatic bladder cancer: results of a large, randomized, multinational, multicenter, phase III study. J Clin Oncol 18:3068–3077