Cancer Chemother Pharmacol (2012) 69:1315–1322
DOI 10.1007/s00280-012-1830-1

ORIGINAL ARTICLE

Gemcitabine in combination with vinorelbine in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer

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Received: 19 November 2011 / Accepted: 16 January 2012 / Published online: 4 February 2012

Abstract
Purpose To evaluate the efficacy and safety of gemcitabine in combination with vinorelbine in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer (MBC).
Patients and methods Elderly patients with MBC received gemcitabine 1,000 mg m^{-2} and vinorelbine 25 mg m^{-2} on days 1 and 8 every 3 weeks for a maximum of 6 cycles. The primary end points were objective response and toxicity. The secondary end points included progression-free survival (PFS), overall survival (OS), and prognostic factors associated with disease control, PFS, and OS.
Results Fifty-one patients with a median age of 73 years (range, 65–84 years) were included. The response rate according to Response Evaluation Criteria in Solid Tumors was 33.3% (95% confidence interval [CI], 20.4 to 46.2%). At a median follow-up of 16.2 months, median PFS and OS were 6.2 (95% CI, 4.6 to 7.8) and 17.0 months (95% CI, 14.5 to 19.5), respectively. Grade 3 to 4 adverse events included neutropenia (25.5%), anemia (13.7%), thrombocytopenia (9.8%), fatigue (5.9%), constipation (3.9%), neuropathy (3.9%), and hepatotoxicity (3.9%). Neutropenic fever occurred in 2 patients. There was one toxic death due to massive gastrointestinal hemorrhage. The study of prognostic factors did not reveal any predictive factor of disease control, while response to treatment and Eastern Cooperative Oncology Group performance status was the main factor conditioning PFS and OS, respectively.
Conclusion Gemcitabine in combination with vinorelbine is active and safe in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer.

Keywords Gemcitabine · Vinorelbine · Chemotherapy · Elder · Metastatic breast cancer

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Introduction

Breast cancer tops both the incidence and mortality of malignant diseases in women worldwide, accounting for 23% of the total new cancer cases and 14% of the total cancer deaths in 2008 [1]. The incidence of breast cancer increases with age [2]. Because of a progressively aging population, it can be expected that the number of elderly breast cancer patients will increase in the future [3]. However, the therapeutic approach for elderly breast cancer patients is currently not based on the reliable evidence, because elderly patients are often excluded from or underrepresented in clinical trials [4]. Barriers to the enrollment of elderly patients are mainly based on the bias that elderly patients will not tolerate or benefit from chemotherapy, in which elderly patients are often

accompanied with impaired bone marrow function, abnormal drug metabolism, and high rates of comorbidities, which can increase the incidence of treatment-related complications [5]. So, there is an urgent need to develop and institute appropriate standards of care for elderly women with breast cancer.

Anthracycline and taxane have been widely accepted as the two most active chemotherapeutic agents for breast cancer. Their increasing use in the adjuvant and neoadjuvant setting has led to a growing number of patients who are pretreated with them or no longer tolerate them, making the subsequent treatment a concern.

Gemcitabine and vinorelbine, either alone or in combination, have shown activity in metastatic breast cancer (MBC) pretreated by anthracycline and taxane [6–21]. Single agent gemcitabine can achieve disease control rate of 35%, median progression-free survival (PFS) of 4.5 months and median overall survival (OS) of 9.8 months on relapsing or failing of both anthracycline and taxane [6]. Gemcitabine is suitable for elderly patients due to its low toxic profile, manifested by the mild myelosuppression and minimal nonhematologic toxicity [7–9].

Single agent vinorelbine is active for MBC pretreated by anthracycline and taxane, with disease control rate of 49%, median PFS of 3.8 months, and median OS of 12.6 months [6, 10–15]. Vinorelbine is well tolerated in the elderly patient population, with noncumulative granulocytopenia and neurotoxicity as the main dose-limiting toxicities [22]. Gemcitabine plus vinorelbine have shown activity in anthracycline- and taxane-pretreated MBC in previous studies [16–21]. However, elderly patients only constituted a minority in these trials, which made it difficult to extrapolate the results to the whole patient group.

Our study aimed to investigate the efficacy and safety of gemcitabine plus vinorelbine in elderly patients with anthracycline- and taxane-pretreated MBC, and to search for prognostic factors for disease control, PFS, and OS.

Patients and methods

Eligibility criteria

Eligibility criteria included the following: women; aged ≥65; histologically proven MBC with evidence of disease progression; at least one measurable lesion; Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; normal hepatic, renal and bone marrow functions; expected life expectancy ≥3 months; previously treated with anthracycline- and taxane-based chemotherapy for metastatic disease or as adjuvant/neoadjuvant treatment; no central nervous system metastasis; no serious concurrent medical illness; no history of other malignancies; no simultaneous or previous radiotherapy on the assessable lesion; and no prior exposure to vinorelbine or gemcitabine. Patients had to have discontinued previous treatment for a minimum of 4 weeks. Concomitant radiotherapy or hormone therapy was not permitted. Multidimensional geriatric assessment (MGA) was also performed at baseline [23], and only those fit patients were included into this study. The study was approved by the Ethics Committees of Shandong Tumor Hospital and Institute. Written informed consent was obtained from all patients before their entry into the study, and the study was carried out in accordance with Helsinki Declaration.

Treatment plan

This was a monoinstitutional, nonrandomized, prospective phase II study. All patients received gemcitabine (1,000 mg/m^2 in a 30-minute intravenous infusion) and vinorelbine (25 mg/m^2 in a 10-minute intravenous infusion) on days 1 and 8 every 21 days. All patients received 5-HT$_3$ antagonist for emesis prophylaxis. Patients were scheduled to receive a maximum of 6 cycles, and chemotherapy was stopped in case of disease progression, patient refusal, or unacceptable toxicity. If the disease progressed, it could be treated with other chemotherapy regimens or endocrine therapy at the investigators' discretion.

Assessment of response and toxicity

All measurable lesions were evaluated at baseline by spiral computer tomography scans and were repeated every 2 cycles to document complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to Response Evaluation Criteria in Solid Tumors (RECIST) [24]. Furthermore, specific organ response (including lymph node, lung, skeleton, liver, and skin) was also evaluated by RECIST, which only included the metastatic lesion in this organ. When multiple lesions were identified, up to ten biggest measurable target lesions were taken to represent all the lesions involved. Tumor response per treatment line was also recorded.

Adverse events were classified according to National Cancer Institute Common Toxicity Criteria (NCI-CTC) version 3.0 [25]. For each patient and each kind of toxicity, the worst degree of toxicity throughout the treatment was recorded.

Complete blood cell counts with differential counts analyses were repeated once to twice a week. When neutropenia, thrombocytopenia, or anemia grade ≥2 developed, the use of recombinant human granulocyte colony-stimulating factor (G-CSF), thrombopoietin (TPO) or interleukin-11 (IL-11), or erythropoietin (EPO) was

permitted. Prophylactic administrations of G-CSF were not performed.

Dose modification

Treatment interruption or dose adjustments were made on the basis of hematologic and nonhematologic toxicities. Treatment was interrupted in cases of grade 2 or higher toxicities (with the exception of alopecia, nausea/vomiting) and was not resumed until the adverse event was improved to grades 1 or 0. In case of grade 0–2 toxicity, chemotherapy was not adjusted for the next cycle, but in grade 3 toxicity (except nausea/vomiting or alopecia) a 25% dose reduction of both gemcitabine and vinorelbine was instituted for the next cycle. In case of grade 4 hematologic toxicity, a 50% dose reduction of both drugs were applied, while the patient was out of study in case of any grade 4 nonhaematological toxicity.

Statistical analysis

The primary end point of the study was to determine the response rate and toxicity. The secondary end points included PFS, OS, and prognostic factors associated with disease control, PFS, and OS. The required number of patients for this study was calculated according to Simon optimal two-stage designs [26], with predetermined $(\alpha) = 0.05$, power $1 - (\beta) = 0.80$. The null hypothesis was that the response rate was 20% versus the alternative that it was at least 40%, and then 13 patients were to be enrolled during the first step and an additional 30 patients during the second step. If three or less responses occurred among the first 13 patients or 12 or less responses in the total population of 43 patients, the treatment had to be judged ineffective and the study had to be terminated. Assuming a dropout rate of 15%, a total of 51 patients were to be enrolled.

PFS was measured from the date therapy was initiated to the date of documented disease progression or death. OS was measured from the date therapy was initiated to the date of death or final follow-up. PFS and OS were calculated via the Kaplan–Meier method. Pearson's χ^2 test was used to investigate the influence of baseline characteristics on disease control (CR + PR + SD vs. PD), unless a group contained five individuals or less, when Fisher's exact test was used. The baseline characteristics included into the analysis were age ($\leq$ median vs. >median), ECOG performance status (0 vs. $\geq$1), estrogen receptor status (negative vs. positive), progestin receptor status (negative vs. positive), human epidermal growth factor receptor-2 (negative vs. positive), associated chronic diseases (absence vs. presence), visceral metastasis (absence vs. presence), number of metastatic locations ($\leq$2 vs. >2), and treatment line (first-line vs. $\geq$ second-line). Baseline characteristics and tumor response (CR + PR vs. SD + PD) were analyzed for PFS and OS by Log-rank test. Cox proportional hazards multivariate modeling was used to identify factors that independently predicted PFS and OS. All data were analyzed by SPSS for windows version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patients' characteristics

Fifty-one patients were enrolled between January 2005 and December 2009 in Shandong Tumor Hospital and Institute. The study was not suspended for interim evaluation because four responses had been documented by the end of the first stage of accrual. Table 1 provides baseline demographic data. Median patient age was 73 years (range, 65–84 years). The main metastatic locations were lymph nodes (62.7%), lung (52.9%), and bone (31.4%). Twenty-eight patients (54.9%) received gemcitabine plus vinorelbine in the first-line setting. The median time elapsed from adjuvant or neoadjuvant therapy with anthracycline and taxane was 3.8 years (range, 0.4–6.9). Twenty-one patients (41.2%) presented with one or more concomitant chronic diseases, primarily hypertensive cardiovascular disease (8 patients, 15.7%), diabetes mellitus (5 patients, 9.8%), and chronic obstructive pulmonary disease (3 patients, 5.9%). Two patients (3.9%) had both hypertensive cardiovascular disease and diabetes mellitus. Two patients suffered from Parkinson's disease, and rheumatoid disease, respectively.

Efficacy

In total, 197 cycles of chemotherapy (median 4, range 1–6 cycles) were delivered. Twenty patients (39.2%) completed all cycles of treatment. Reasons for early treatment discontinuation were patients' withdrawal of consent in 12 patients (23.5%), excessive complication or toxicity in 10 patients (19.6%), disease progression in 8 patients (15.7%), and follow-up loss in 1 patient (2.0%).

Among 51 enrolled patients, 3 patients received only one cycle of chemotherapy and could not be evaluated for response, for follow-up loss, withdrawal of study due to treatment-related nausea/vomiting, and toxic death for massive gastrointestinal bleeding, respectively. This patient did not go to hospital or follow the recommended hemostasis and, thus, died at home. No postmortem was done after death.

Among 48 evaluable patients, 1 patient achieved CR (1.9%) and 16 patients (31.4%) PR, yielding a response rate (RR) of 33.3% (95% CI, 20.4 to 46.2%). Twenty-six

Table 1 Patients' baseline characteristics ($n = 51$)

Characteristics	Number (%)
Age (years)	
Median	73
Range	65–84
ECOG performance status	
0	29 (56.9)
1	17 (33.3)
2	5 (9.8)
Estrogen receptor status	
Positive	33 (64.7)
Negative	15 (29.4)
Unknown	3 (5.9)
Progestin receptor status	
Positive	32 (62.7)
Negative	16 (31.4)
Unknown	3 (5.9)
HER-2 status	
Positive	6 (11.8)
Negative	40 (78.4)
Unknown	5 (9.8)
Pathology	
Duct	44 (86.3)
Lobe	4 (7.8)
Others	3 (5.9)
Number of metastatic sites	
1	12 (23.5)
2	15 (29.4)
≥3	24 (47.1)
Site of metastasis	
Lymph nodes	32 (62.7)
Lung	27 (52.9)
Skeleton	16 (31.4)
Liver	15 (29.4)
Skin	12 (23.5)
Treatment line	
First line	28 (54.9)
Second line	17 (33.3)
≥Third line	6 (11.8)
Number of concomitant disease	
0	30 (58.8)
≥1	21 (41.2)

ECOG Eastern cooperative oncology group; *HER-2* human epidermal growth factor receptor 2

patients (51.0%) had stable disease, and 8 patients (15.7%) had progressive disease. Stratified by treatment line, disease response was obtained in 10 out of 28 patients (35.7%) in the first-line setting, 6 out of 17 patients (35.3%) in the second-line, and 1 out of 6 patients (16.7%) in ≥ the third-line. As outlined in Table 2, responses were seen in all disease sites, but particularly in lymph node (43.7%) and lung (40.8%). Whereas, liver and skeleton metastases responded poorly, with RR 20.0% and 12.5%, respectively.

At a median follow-up of 16.2 months, median PFS and OS were 6.2 months (95% CI, 4.6–7.8) and 17.0 months (95% CI, 14.5–19.5), respectively. PFS and OS time curves were shown in Figs. 1 and 2.

Toxicity

All patients could be evaluated for toxicity. Treatment was generally well tolerated, and every grade of hematologic and nonhematologic toxicities was reported in Table 3. The majority of adverse events were grade 1–2 in severity.

The predominant toxicities were hematologic, manifested by high incidence of neutropenia (80.4%), anemia (62.7%) and thrombocytopenia (21.5%). Grade 3/4 neutropenia occurred in 13 patients (25.5%). However, it was generally uncomplicated and rapidly reversible. Only two patients developed neutropenic fever and were successfully treated with G-CSF and antibiotics without further complication. Anemia was frequent but generally mild to moderate, with grade 1/2 in 25 patients (49.0%) and grade 3/4 in 7 patients (13.7%). Thrombocytopenia was noted in about one-fourth of patients, with grade 3/4 in 5 patients (9.8%).

Nonhematologic toxicities were acceptable. The most common nonhematologic toxicities were nausea/vomiting (56.9%), fatigue (51.0%), hepatotoxicity (27.5%), constipation (25.5%), and neurotoxicity (21.6%). Grade 4 nonhematologic toxicities could only be seen in 1 case for elevation of liver enzymes. Yet it was hard to interpret, because the patient had a progressive liver metastasis. Grade 3 toxicities were reported for fatigue in 3 patients (5.9%), for constipation and peripheral neuropathy in 2 patients (3.9%) each, and for hepatotoxicity in 1 patient (2.0%).

Drug dose was reduced to 75% of the starting dose in 17 patients, for hematologic toxicity in 15 patients, and nonhematologic toxicity in 2 patients. Two patients required a second dose reduction for hematologic toxicity, which meant the dose was reduced to 50% of the initial dose.

A hypersensitivity reaction was observed in 1 patient during administration of gemcitabine in the second cycle. The symptoms include flushing, tachycardia, pruritus, and chest discomfort and were released by discontinuation of gemcitabine and administration of steroids and antihistamines.

Prognostic factors

Patients were dichotomized into disease control group (CR + PR + SD) and uncontrolled group (PD). χ^2 test

Table 2 Response according to disease site

Site	Number of patients (%)				
	Complete response	Partial response	Stable disease	Progressive disease	Not evaluable
Lymph nodes	1 (3.1)	13 (40.6)	8 (25.0)	8 (25.0)	2 (6.3)
Lung	0	11 (40.8)	9 (33.3)	6 (22.2)	1 (3.7)
Skeleton	0	2 (12.5)	12 (75.0)	2 (12.5)	0
Liver	0	3 (20.0)	7 (46.7)	4 (26.6)	1 (6.7)
Skin	0	3 (25.0)	5 (41.7)	3 (25.0)	1 (8.3)

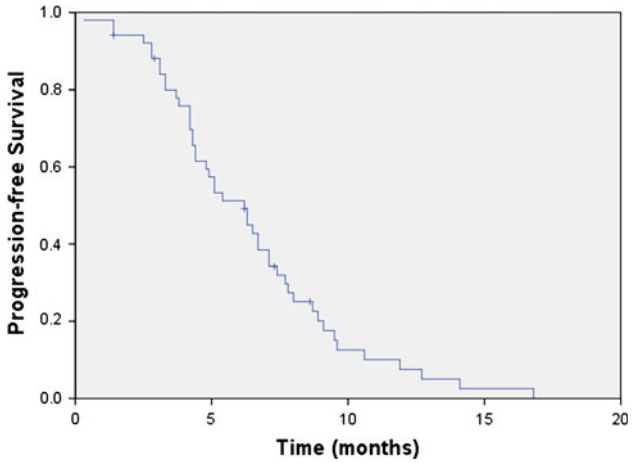

Fig. 1 Kaplan-Meier curves of progression-free survival

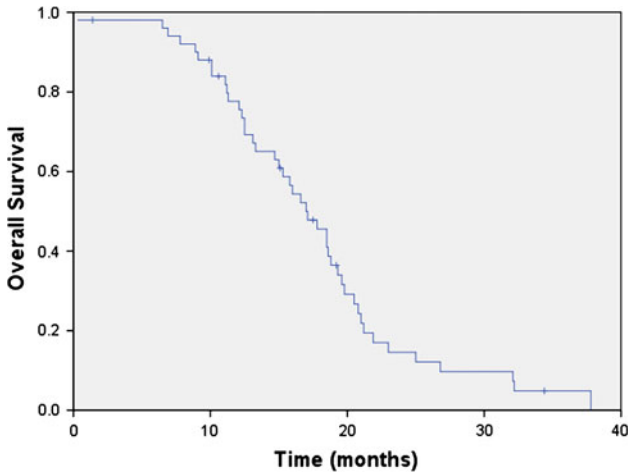

Fig. 2 Kaplan-Meier curves of overall survival

revealed no predictive factors for disease control. Response to chemotherapy was found to be the only one prognostic variable for PFS ($P = 0.013$; hazard ratio = 2.3; 95% CI, 1.2–4.4). ECOG performance status of 0, less than 3 metastatic locations, and absence of visceral metastasis were associated with an increase in overall survival ($P = 0.018$, $P = 0.041$, and $P = 0.049$, respectively). In the multivariate analysis, ECOG performance status was the only predictive factor for OS ($P = 0.007$, hazard ratio = 2.4, 95% CI, 1.3–4.7).

Table 3 Incidence of adverse events ($n = 51$)

Adverse events	Number of patients (%)			
	Grade 1	Grade 2	Grade 3	Grade 4
Hematologic				
Leukopenia	12 (23.5)	13 (25.5)	10 (19.6)	4 (7.8)
Neutropenia	11 (21.6)	17 (33.3)	11 (21.6)	2 (3.9)
Anemia	15 (29.4)	10 (19.6)	7 (13.7)	0
Thrombocytopenia	4 (7.8)	2 (3.9)	5 (9.8)	0
Nonhematologic				
Nausea/vomiting	15 (29.4)	14 (27.5)	0	0
Fatigue	17 (33.3)	6 (11.8)	3 (5.9)	0
Hepatotoxicity	9 (17.6)	3 (5.9)	1 (2.0)	1 (2.0)
Constipation	6 (11.8)	5 (9.8)	2 (3.9)	0
Neuropathy	6 (11.8)	3 (5.9)	2 (3.9)	0
Mucositis	6 (11.8)	4 (7.8)	0	0
Alopecia	5 (9.8)	5 (9.8)	0	0
Diarrhea	4 (7.8)	3 (5.9)	0	0

Discussion

Despite great improvements have been made in the treatment of MBC, there are still several unmet needs. Among them are to determine appropriate standard of care for those with previous exposure to anthracycline and taxane and to develop predictive factors, which will help to select patients who are most likely to benefit from a particular agent and to avoid unnecessary toxicity of ineffective treatments. Our study tried to investigate the efficacy and toxicity of combination therapy of gemcitabine and vinorelbine in elderly patients with anthracycline- and taxane-pretreated MBC and to explore reliable prognostic factor for disease control, PFS, and OS.

In fact, the use of combination therapy in the palliative setting is not well argued. An overview of randomized

phase II and III trials [18, 20, 27] comparing gemcitabine in combination with vinorelbine versus single agent or sequential cytotoxic agent demonstrated conflicting results. Some studies showed that combination treatments were associated with a significant prolongation of PFS and significantly higher objective response rate, while others not. In a phase III trial, gemcitabine and vinorelbine combination therapy was shown to be superior to single agent vinorelbine in both PFS (median 6.0 months vs. 4.0 months, $P = 0.0028$) and objective response rate (36 vs. 26%, $P = 0.093$), with manageable toxicities [20]. In a phase II study comparing gemcitabine and vinorelbine combination therapy with sequential gemcitabine and vinorelbine therapy, although no difference in efficacy was found between the two arms, patients in the combination arm reported an improvement in quality of life in the presence of similar episodes of adverse events [18]. Another phase III study of gemcitabine plus vinorelbine versus single agent capecitabine demonstrated no superiority of doublet over single agent in terms of objective response, or PFS. Given the favorable toxicity profiles and convenient administration, single agent capecitabine was recommended for compliant patients [27]. To our knowledge, up to now there is no head-to-head comparison of gemcitabine plus vinorelbine versus sequential or single agent in elderly patients.

Our study showed that gemcitabine plus vinorelbine was an effective and safe therapeutic option, yielding a response rate of 33.3%, median PFS 6.2 months, and median OS 17.0 months. Response rates with gemcitabine/vinorelbine regimen range between 22% and 36% in the reviewed literature [16–21]. The 33.3% of response rate observed in our study was comparable with the efficacy seen in previous trials that composed of nonelderly patients [16–21]. This age-independent benefit of chemotherapy is consistent with other studies [28, 29]. A retrospective analysis of elderly patients with MBC managed with palliative chemotherapy showed that disease control was comparable to those reported in younger patients [28]. Blum et al. made a pooled analysis of patients with MBC treated with capecitabine and found no statistical association between age and response, clinical benefit, or OS [29].

As for tolerability, gemcitabine plus vinorelbine showed manageable hematologic and nonhematologic toxicities. The mild-to-moderate toxicity was important to elderly patients in that quality of life was an important consideration for MBC, which was destined to be incurable. There was one toxic death for massive gastrointestinal hemorrhage. The patient did not seek hospital care or follow doctor's hematostatic instructions and, thus, died at home. For this reason, we must emphasize the importance of selecting patients who are fully aware of the adverse events of treatment and who will cooperate with doctor when potential complications are indicated.

The study of prognosis revealed no predictive factor of disease control, while response to treatment was the only factor conditioning PFS in the univariate analysis. ECOG performance status was an independent prognostic factor of OS in the multivariate analysis, while visceral metastasis and the number of metastatic site were significant only in the univariate analysis. These results were not in accordance with previous study [16], which concluded that estrogen receptor status was an independent predictor for both time to progression (TTP) and OS. We cannot exclude that limited sample size, age, genetic heterogeneity, prior treatment, or chemotherapeutic sensitivity could account for this difference. Furthermore, unlike other studies [30, 31], visceral metastasis no longer correlated clearly with OS, suggesting that this classical poor-prognosis feature may not have a major impact in elderly MBC patients receiving gemcitabine plus vinorelbine.

It should be mentioned that this regimen showed response in all lines of treatment with the highest in the first- and second-line setting and in all sites of metastasis, but particularly in lung and lymph nodes. One advantage of this combination is that both drugs were administered on days 1 and 8 of every 3 weeks cycle, so patients just need to visit hospital twice every three weeks, which does not modify much their daily activities during the treatment period.

It seems that elderly patients should not be excluded from gemcitabine/vinorelbine regimen just because of age. They should be given the same opportunity to receive palliative chemotherapy, but at the same time, proper guidance should be guaranteed and dose modification should be made when necessary.

Taken together, the response rate of gemcitabine/vinorelbine regimen was relatively high, the toxicity was generally acceptable, and median PFS and OS were relatively long; this regimen may be regarded as a valuable alternative to the treatment of elderly MBC patients after anthracycline and taxane regimens. Further evaluation in randomized multicenter trials is warranted.

Acknowledgment We thank Dr. Jun Ren for his assistance during the writing of the article.

Conflict of interest All authors indicated no potential conflicts of interest.

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