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ORIGINAL ARTICLE

Gemcitabine plus capecitabine in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer

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Summary

Purpose: *To investigate the efficacy and safety of gemcitabine plus capecitabine in elderly patients with anthracycline- and taxane-pretreated metastatic breast cancer (MBC).*

Methods: *Eligible patients received gemcitabine 1,000 mg/m^2 on days 1 and 8, and capecitabine 1,000 mg/m^2 twice daily on days 1-14. The treatment was repeated every 3 weeks for a maximum of 6 cycles. The primary endpoint was objective response rate (ORR). The secondary endpoint included progression-free survival (PFS), overall survival (OS), and toxicity.*

Results: *Forty-eight patients with a median age of 72 years (range, 65-83) were included. The ORR according to Response Evaluation Criteria in Solid Tumors (RECIST) was 29.2% (95% confidence interval [CI], 16.3% to 42.1%). After a median follow-up of 17.4 months, median PFS and OS were 6.4 months (95% CI, 5.2-7.6) and 18.0 months (95% CI, 14.8-21.2), respectively. Grade 3 to 4 adverse events included neutropenia (20.8%), asthenia (8.3%), hand-foot syndrome (6.3%), abnormal liver function (6.3%), diarrhea (6.3%), constipation (2.1%) and thrombocytopenia (2.1%). Neutropenic fever occurred in one patient.*

Conclusions: *Gemcitabine plus capecitabine are active and safe in elderly patients with anthracycline- and taxane-pretreated MBC.*

Key words: *breast cancer, capecitabine, chemotherapy, elderly, gemcitabine*

Introduction

Breast cancer is the most prevalent malignancy in females worldwide, with an estimated 2 million new cases annually [1]. Due to the expanding aging population in both developing and developed countries, breast cancer is to a large extent a disease of the elderly [2]. The median age at diagnosis is 62 years in the United States and 63 years in Europe [3]. Although 41% of cases occur in women aged 65 or over, only 9% of this population is represented in clinical trials, which has resulted in insufficient evidences to guide appropriate treatment decisions for the elderly group [4]. The degenerated organ function, comorbidity, and drug-drug interaction may be the principal reasons for the underrepresentation.

Advancing age is often associated with favorable tumor characteristics, such as more estrogen receptor positivity, less HER-2/neu overexpression, and lower proliferation indices [5]. However, at the time of diagnosis, older patients are more likely to present with advanced disease stage because of negligence of individual screening and clinical examination of the breast [6]. Breast cancer-related mortality increases with age, after adjusting for comorbidity, which could be partially explained by undertreatment [7].

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Systemic chemotherapy is indicated in patients with hormone receptor-negative, hormone-refractory, rapidly progressing disease, or symptomatic visceral metastases. Anthracyclines and taxanes are the preferred cytotoxic agents in these settings. However, their increasing use in the early stage of disease has led to a growing number of patients who are resistant to them or no longer tolerate them due to the cumulative dose-limiting adverse events, making the subsequent treatment a challenge to the oncologist.

Capecitabine is an oral prodrug that is converted to 5-fluorouracil predominantly in tumors through exploitation of the significantly higher activity of thymidine phosphorylase in tumor tissue compared with healthy tissue. It has received Food and Drug Administration (FDA) approval for anthracycline- and taxane-pretreated metastatic breast cancer (MBC). Capecitabine is generally well tolerated by elderly patients, with diarrhea and hand-foot syndrome as the two most common dose-limiting toxicities [8]. Gemcitabine is a nucleoside analogue of deoxycytidine, with proven efficacy in various cancers including breast cancer. Gemcitabine is generally well tolerated by elderly patients with manageable safety profiles, manifested by mild to moderate hematological and nonhematological toxicities [9]. Both gemcitabine and capecitabine show no cross-resistance to anthracyclines and taxanes, because of their different mechanisms of antitumor activity. Previous studies have shown gemcitabine plus capecitabine is efficacious and safe for anthracycline- and taxane-pretreated MBC [10-13]. However, elderly patients were not well represented in these studies, with the median age between 48 and 55 years, which made it difficult to extrapolate the results to the elderly group. So in this study we investigated the efficacy and safety of gemcitabine plus capecitabine in elderly patients with anthracycline- and taxane-pretreated MBC.

Methods

Patient selection

The main inclusion criteria included the following: female; aged 65 or over; histologically proven breast cancer; clinically confirmed MBC; human epidermal growth factor receptor 2 (HER-2) negative, at least one measurable lesion according to Response Evaluation Criteria in Solid Tumors (RECIST); Eastern Cooperative Oncology Group (ECOG) performance status of 0 to 2; adequate liver, renal and bone marrow functions; estimated life expectancy of at least 3 months; prior treatment with anthracycline- and taxane-containing regimen in the (neo)adjuvant or metastatic setting; at least 1 month since previous chemotherapy or hormonal therapy; no central nervous system metastasis; no history of other malignancies; no prior exposure to capecitabine or gemcitabine, and no previous radiation to the measurable lesion. Signed informed consent was obtained from all patients before enrollment. The study was approved by the Ethics Committees of Shandong Tumor Hospital and Institute, and was conducted according to Declaration of Helsinki.

Treatment plan

This was an open-label, single-center, single-arm, prospective phase II study. Gemcitabine 1,000 mg/m^2 was administered as a 30-min intravenous infusion on days 1 and 8. Capecitabine was given orally at the dosage of 1000 mg/m^2 twice daily on days 1-14. The regimen was repeated every 21 days. 5-HT$_3$ antagonist was routinely given for emesis prophylaxis before each gemcitabine dose. Prophylactic administration of colony-stimulating factors was not allowed. Patients were scheduled to receive a total of 6 cycles in the absence of patient refusal, disease progression, or intolerable toxicity.

Tumor response was assessed every 2 cycles to document complete response (CR), partial response (PR), stable disease (SD), or progressive disease (PD) according to the RECIST [14]. Toxicity was evaluated according to the National Cancer Institute-Common Toxicity Criteria, version 4.0.

Dose modification

Because the dose-limiting toxicities of gemcitabine and capecitabine are well known, treatment interruption and dose adjustment were made considering hematologic and non-hematologic toxicities. If the absolute neutrophil count was reduced to 0.5-1.0×10^9/L or if the platelet count was reduced to 50-100×10^9/L, gemcitabine dose was reduced by 25%. If the neutrophil count was lower than 0.5×10^9/L or the platelet count was lower than 50×10^9/L, gemcitabine dose was reduced by 50%, and capecitabine by 25%. If febrile neutropenia occurred, the doses of both drugs were reduced by 25%.

Capecitabine dose reduction was not indicated for the first appearance of any grade 2 non-haematological adverse events, but was reduced by 25% for the second occurrence of grade 2, or the first occurrence of a grade 3 non-haematological adverse event. Capecitabine dose was reduced by 50% for the third occurrence a grade 2 non-haematological adverse event, or the second occurrence of a grade 3 event. Capecitabine was discontinued permanently if the adverse event did not resolve to grade 1 or less within 3 weeks, or if any grade 4 non-hematological adverse events occurred.

Statistics

The primary endpoint of the study was the objective response rate (ORR). The secondary endpoints included progression-free survival (PFS), overall survival (OS), and toxicity. The expected number of patients for enrollment was calculated according to Simon optimal two-stage designs [15], with a two-sided alpha level of 0.05 and a power of 0.8. The null hypothesis was that the objective response rate was ≤ 20% versus the alter-

native that it was ≥ 40%, and then 13 patients were to be included during the first stage. If ≤ 3 responses were observed among the stage, the trial was considered to be of no further interest. If ≥ 4 patients responded, an additional 30 eligible patients would be accrued during the second stage. If ≤ 12 responses occurred among the total of 43 patients, the regimen would be judged ineffective. Assuming a dropout rate of 10%, a total of 48 patients were to be enrolled.

PFS was defined as the period from the date therapy was initiated to the date of documented disease progression or death. OS was defined as the period from the first day therapy was given to the date of death or last follow-up. Kaplan-Meier method was used to calculate PFS and OS and log-rank test to estimate differences between groups. Statistical analyses were carried out by SPSS for windows version 16.0 (SPSS Inc., Chicago, IL, USA).

Results

Patient characteristics

From January 2010 to December 2015, 48 patients were consecutively enrolled into the study. The trial was not stopped for interim evaluation because 4 responses had been documented during the first stage of enrolment. The main baseline characteristics of the patients are summarized in Table 1. The median age was 72 years (range, 65-83). Common metastatic locations included lymph nodes (60.4%), lung (54.2%), bone (39.6%), and liver (33.3%), with multiple metastases in 70.8% of the patients. More than half of patients (52.1%) had received no prior systemic chemotherapy for metastatic disease. Nineteen patients (39.6%) received prior fluoropyrimidine-based regimen; of these, 13 patients (27.1%) received the therapy in the adjuvant setting, and 6 patients (12.5%) in the metastatic setting.

Efficacy

Forty-eight patients received a total of 183 treatment cycles (median 4, range 1-6). Eighteen patients (37.5%) received 6 cycles of chemotherapy. Reasons for early treatment discontinuation included disease progression in 12 patients (25.0%), patients' refusal in 10 (20.8%), adverse events in 7 (14.6%), and lost to follow-up in 1 patient (2.1%).

Among the 48 patients enrolled, 3 patients received only one treatment cycle and thus were not eligible for response evaluation, for follow-up loss, treatment-related diarrhea, and withdrawn of consent, respectively. In an intention-to-treat analysis, no patient achieved CR and 14 patients (29.2%) PR, which led to an ORR of 29.2% (95% confidence interval [CI], 16.3% to 42.1%). Nineteen patients (39.6%) and 12 patients (25.0%) had SD and PD, respectively. After a median follow-up of 17.4 months, median PFS and OS were 6.4 months (95% CI, 5.2-7.6) and 18.0 months (95% CI, 14.8-21.2), respectively. PFS and OS time curves are shown in Figures 1 and 2.

Stratified by treatment line, objective response was obtained in 9 out of 25 patients (36.0%) in the first-line setting, and 5 out of 23 patients (21.7%) in the second-line and beyond. For patients who had previously received fluoropyrimidine-based regimen, responses could be seen in 3 of 13 patients (23.1%) with previous exposure in the adjuvant setting, and 1 of 6 patients (16.7%) in the metastatic setting (p=0.75). Both PFS and OS were shorted in those with previous exposure in the metastatic setting than in those in the adjuvant setting (PFS, median 5.7 vs. 7.2 months, p=0.750; OS, median 13.1 vs. 18.0 months, p=0.504).

Table 1. Baseline patient characteristics (n=48)

Characteristics	*Number of patients n(%)*
Age (years)	
Median	72
Range	65-83
ECOG performance status	
0	23 (47.9)
1	22 (45.8)
2	3 (6.3)
Estrogen receptor status	
Positive	36 (75.0)
Negative	12 (25.0)
Progesterone receptor status	
Positive	33 (68.8)
Negative	15 (31.2)
Number of metastatic sites	
1	14 (29.2)
2	12 (25.0)
≥3	22 (45.8)
Metastatic site	
Lymph node	29 (60.4)
Lung	26 (54.2)
Bone	19 (39.6)
Liver	16 (33.3)
Previous endocrine therapy	39 (81.3)
Previous radiotherapy	20 (41.7)
Previous fluoropyrimidines	19 (39.6)
Treatment line	
First line	25 (52.1)
Second line	14 (29.2)
≥Third line	9 (18.7)

ECOG: Eastern Cooperative Oncology Group

Toxicity

All patients could be assessed for toxicities. The majority of toxicities were grade 1 to 2 in intensity, and grade 3 to 4 toxicities were relatively rare, as shown in Table 2.

As expected, neutropenia was the predominant hematological toxicity, with grade 1 to 2 in 14 patients (29.2%), and grade 3 to 4 in 10 patients (20.9%). One patient experienced febrile neutropenia. Anemia and thrombocytopenia were mild. No patient experienced grade 3 or higher anemia, whereas one patient experienced grade 3 thrombocytopenia.

Common nonhematological toxicities included asthenia (66.7%), hand-foot syndrome (39.6%), abnormal liver function (35.4%), diarrhea (22.9%), nausea/vomiting (20.8%), and stomatitis (20.8%), each of which affected more than 20% of all patients. Asthenia, which occurred in more than half of the total patients, might be related to anemia. But it was difficult to determine whether asthenia was cancer-related or treatment-related. The overall incidence of grade 3 or 4 adverse events was low. Grade 4 nonhematological toxicities could only be seen in one case for diarrhea. Grade 3 nonhematological toxicities were reported for asthenia in 4 patients (8.3%), for hand-foot syndrome and abnormal liver function in 3 patients (6.3%) each, for diarrhea in 2 patients (4.2%), and for constipation in 1 patient (2.1%). The incidence of grade 3 or 4 adverse events was also analyzed according to age category. Nine (30.0%) of 30 patients older than 70 years developed grade 3 or 4 adverse events, compared with 3 (16.7%) of 18 patients aged 65 to 70 years (p=0.302). There was no treatment-related death.

The dosage of gemcitabine was reduced to 75% of the starting dose in 8 patients, for neutropenia in 7 patients and thrombocytopenia in 1 patient. Capecitabine dosage was reduced to 75% of the starting dose in 6 patients, for hand-foot syndrome in 3 patients, abnormal liver function in 2 patients, and diarrhea in 1 patient. No patient needed further reduction.

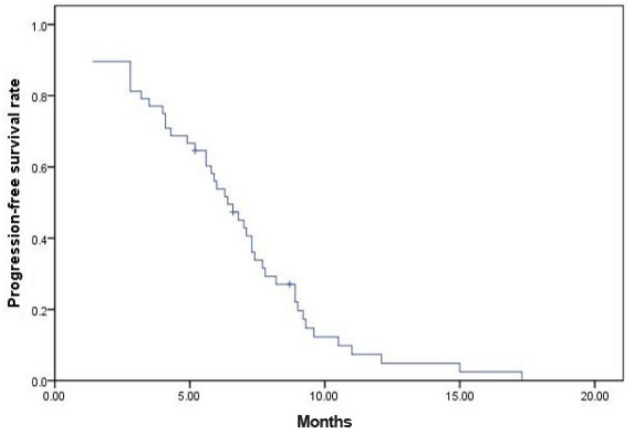

Figure 1. Kaplan-Meier curve of progression-free survival.

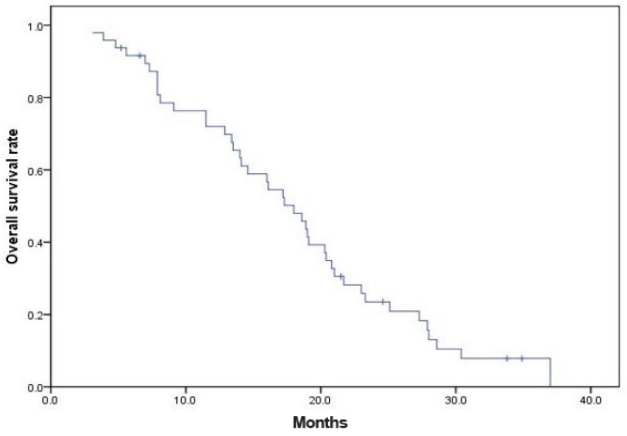

Figure 2. Kaplan-Meier curve of overall survival.

Table 2. Incidence of adverse events (n=48)

Adverse events	*Number of patients (%)*			
	Grade 1 *n (%)*	*Grade 2* *n (%)*	*Grade 3* *n (%)*	*Grade 4* *n (%)*
Hematologic				
Neutropenia	9 (18.8)	5 (10.4)	7 (14.6)	3 (6.3)
Anemia	10 (20.8)	1 (2.1)	0	0
Thrombocytopenia	3 (6.3)	2 (4.2)	1 (2.1)	0
Nonhematologic				
Asthenia	19 (39.6)	9 (18.8)	4 (8.3)	0
Hand-foot syndrome	11 (22.9)	5 (10.4)	3 (6.3)	0
Abnormal liver function	8 (16.7)	6 (12.5)	3 (6.3)	0
Diarrhea	5 (10.4)	3 (6.3)	2 (4.2)	1 (2.1)
Nausea/vomiting	7 (14.6)	3 (6.3)	0	0
Stomatitis	6 (12.5)	4 (8.3)	0	0
Constipation	4 (8.3)	2 (4.2)	1 (2.1)	0

Discussion

Despite the increasing incidence of breast cancer, death rates are falling due to early detection and systemic therapy. However, great advance in the elderly patient is not well documented, and considerable controversy persists in what constitutes the appropriate care. Because clinical trials concerning elderly cancer patients are scarce, the treatment is often based on the intuitive judgment of the oncologist rather than on evidence-based guidelines. Elderly patients are at risk of either empirical under-treatments resulting in poor survival or excessive toxicity from standard therapy [16].

To date, there is no widely accepted standard of chemotherapy for anthracycline- and taxane-pretreated MBC. Single agent capecitabine is the current reference treatment, with a response rate of about 20% [17]. Gemcitabine monotherapy had also shown efficacy in previous studies, with ORR of 17-20%, median PFS of about 4 months and median OS of 9.5-11 months [18]. In addition, capecitabine has shown synergistic effects as well as nonoverlapping safety profile when used in combination with gemcitabine. In fact, gemcitabine and capecitabine combination chemotherapy resulted in an ORR of 10-49%, median time to progression (TTP) of 4.3-6 months and median OS of 10-25.1 months in patients with anthracycline- and taxane-pretreated MBC [10-13].

In our study, no CR was observed and 14 of 48 patients achieved PR, which led to an ORR of 29.2%. Response could not only be seen in those receiving the regimen in the first-line setting, but also in the second-line setting. Median PFS and OS were 6.4 months and 18.0 months, respectively. The 29.2% of ORR was comparable with previous trials that were composed of nonelderly patients [10-13]. This age-independent benefit of chemotherapy is in accordance with other studies [4,19]. It seemed that older patients could benefit the same from standard chemotherapy as the younger counterparts, and age alone should not limit treatment options.

As for the safety data, the incidence of grade 3 or 4 toxicities was not common. It should be considered that the vast majority of patients (68.8%) enrolled into the study were 70 years of age or older. We found the incidence rate of grade 3 or 4 adverse events in patients aged >70 was higher than those aged 65-70 (30.0% vs. 16.7%), although no statistical difference was reached (p=0.302). It is known that degenerated physiologic functions during aging could affect the pharmacokinetics and pharmacodynamics of chemotherapeutic drugs, leading to a narrowing of the therapeutic margin and an increase in toxicity [20]. One patient developed grade 4 diarrhea in the second cycle, manifested by more than 10 stools per day, electrolyte disturbance, and hemodynamic collapse. This patient was successfully managed by drug interruption, fluid resuscitation and antidiarrheal agent. So special attention should be paid to diarrhea, which, if not quickly treated, can be fatal for elderly patients. Because MBC is incurable, tolerable toxicity was important in that quality of life was an important consideration.

In our study, we can see inter-individual difference in chemotherapeutic response and toxicities. Genetic polymorphisms, which can affect drug pharmacokinetics or pharmacodynamics, could partially account for the differences. Single nucleotide polymorphisms (SNPs) of enzymes responsible for capecitabine activation and metabolism, such as DPYD variants *2A (rs3918290), *13 (rs55886062), −2846A>T (rs67376798) and −1236G>A/HapB3 (rs56038477), may influence treatment outcomes [21]. SNPs of cytidine deaminase, the enzyme responsible for the liver disposition of gemcitabine, could also act as a marker for clinical outcome [22]. And the different responses to the treatment might also be related to the different previous and subsequent treatments of patients, such as endocrine therapy, chemotherapy and radiotherapy.

It seems that vulnerable elderly patients could benefit the same from gemcitabine/capecitabine regimen as the younger patients, and should not be excluded just because of age. They should be given the same opportunity to receive palliative chemotherapy, but at the same time, proper guidance of hematological and nonhematological toxicities should be guaranteed and dose adjustment or interruption should be made when necessary.

Conclusion

Given the relatively high response rate, acceptable toxicities, and relatively long median PFS and OS, gemcitabine plus capecitabine regimen should be regarded as a valid treatment option for elderly patients with MBC who were previously treated with anthracyclines and taxanes. Further evaluation in large randomized multicenter trials is warranted.

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Conflict of interests

The authors declare no conflict of interests.

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