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Gemcitabine and Carboplatin in Intensively Pretreated Patients with Metastatic Breast Cancer

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Key Words
Gemcitabine · Carboplatin · Anthracycline resistance · Metastatic breast cancer

Abstract
Background: Patients with metastatic breast cancer (MBC) are increasingly exposed to anthracyclines and taxanes either during treatment of primary breast cancer or during initial therapy of metastatic disease. The combination of gemcitabine and carboplatin was therefore investigated as an anthracycline- and taxane-free treatment option. ***Patients and Methods:*** MBC patients previously treated with chemotherapy were enrolled in a multicenter phase II study. Treatment consisted of gemcitabine (1,000 mg/m^2 i.v. on days 1 and 8) and carboplatin (AUC 4 i.v. on day 1) applied every 3 weeks. ***Results:*** Thirty-nine patients were recruited, and a total of 207 treatment cycles were applied with a median of 5 cycles per patient. One complete response and 11 partial responses were observed for an overall response rate of 31% (95% CI: 17–48%). Twelve patients (31%) had stable disease. Median time to progression was 5.3 months (95% CI: 2.6–6.7 months) and median overall survival from start of treatment was 13.2 months (95% CI: 8.7–16.7 months). Grade 3/4 hematological toxicity included leukopenia (59%/5%), thrombocytopenia (26%/23%) and anemia (10%/0%). Nonhematological toxicity was rarely severe. ***Conclusion:*** Combination chemotherapy with gemcitabine and carboplatin is an effective and generally well-tolerated treatment option for intensively pretreated patients with MBC. Due to a considerable incidence of severe thrombocytopenia it would be reasonable to consider starting gemcitabine at the lower dose level of 800 mg/m^2.

Introduction

As anthracycline- and also taxane-based regimens have become a standard of care for patients with primary breast cancer in the neoadjuvant and adjuvant setting, the number of patients who have already been exposed to these drugs in the metastatic stage is increasing. Hence, the evaluation of alternative treatment strategies not cross-resistant to anthracyclines or taxanes is mandatory. At the same time, it is important to ensure that efficacy is improved at the lowest cost to quality of life.

Gemcitabine as a single agent has induced overall response rates of 0–37% in first-line treatment, whereas the response rates in the second- or third-line therapy were

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26 and 13% [1–5]. In studies limited to second- or third-line therapy after anthracycline and/or taxane exposure, response rates of 0–29% and median time to progression of 2– 6 months were reached [3–5].

Gemcitabine is an excellent choice for combination therapy because of its unique mechanism of action and its favorable profile of side effects. The combination of gemcitabine and cisplatin was shown to be effective in several trials, inducing response rates between 30 and 52% in patients pretreated with taxanes and/or anthracyclines [6–10].

To improve on tolerability and feasibility of the regimen, carboplatin may be the more appropriate choice for treatment of metastatic disease. In four phase II trials of previously untreated patients with metastatic breast cancer (MBC), single agent carboplatin induced objective response rates between 8 and 35% [11–14]. Studies performed in various solid tumor types indicate comparable activity of cisplatin and carboplatin [15, 16].

It appears that resistance to platinum salts is induced by pretreatment, possibly by an upregulation of DNA repair. Gemcitabine, a known inhibitor of DNA repair, may overcome this form of resistance and thus provides an excellent rationale for the combination of both agents. Exposure to platinum salts causes an activation of DNA repair polymerases and thereby enhances the incorporation of gemcitabine triphosphates into DNA repair patches. Once integrated into DNA, gemcitabine is not readily recognized and excised by proofreading exonucleases and may trigger signaling pathways leading to apoptosis.

Several considerations support the use of gemcitabine and a platinum salt in the salvage treatment of MBC. First, in vitro studies indicate additive or synergistic activity which was most pronounced in platinum-resistant cell lines and was found to be due to an increased formation and an impaired repair of platinum-DNA adducts [17, 18]. Second, gemcitabine and carboplatin are usually not included into adjuvant or neoadjuvant chemotherapy. Therefore, resistance to either drug is unlikely to occur. Third, studies investigating the combination have shown minimal overlapping toxicity suggesting an acceptable toxicity profile even in intensively pretreated patients [4, 19–21]. Finally, the addition of trastuzumab to gemcitabine/carboplatin might form an effective triplet combination [22].

The present multicenter phase II study was aimed to evaluate the efficacy and tolerability of gemcitabine applied on days 1 and 8 plus carboplatin applied on day 1 every 3 weeks in previously treated patients with MBC.

Patients and Methods

Patient Population

Thirty-nine patients with histologically confirmed MBC were recruited to participate in a study with a treatment protocol approved by the local ethics committee. All patients were required to give written informed consent prior to study entry.

Prior treatment with chemotherapy, hormonal therapy, immunotherapy or local radiotherapy was allowed. Patients were required with at least one bidimensionally measurable lesion outside a previous radiation port. Other eligibility criteria included age $\geq$18 years, Karnofsky performance status $\geq$70%, minimal life expectancy of 12 weeks, and adequate hematological, renal, cardiac and hepatic function [leukocyte count $\geq 3.0 \times 10^9$/l or absolute neutrophil count $\geq 2 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l; hemoglobin $\geq$8 g/dl; total serum bilirubin $\leq$1.25 $\times$ upper limit of normal (ULN) in the absence of liver metastasis or $\leq$3.0 $\times$ ULN in the presence of liver metastasis; transaminase (ALT, AST) level $\leq$3 $\times$ ULN in the absence of liver metastasis or $\leq$5 $\times$ ULN in the presence of liver metastasis; alkaline phosphatase level $\leq$2.5 $\times$ ULN]. Creatinine clearance was required to exceed 60 ml/min.

Patients were not eligible for study enrolment if they were pregnant, lactating or refused effective contraception, and if they had bone metastasis only, known brain metastases or a secondary malignancy, history of another primary malignant disease other than in situ carcinoma of the uterine cervix or adequately treated basal cell skin cancer, active infection or any other concomitant severe clinical condition making implementation of the protocol including prehydration difficult. Administration of other cytotoxic, immune or hormonal agents or radiation therapy was not permitted during the study, with the exception of contraceptives, corticosteroids given as antiemetic treatment, or local palliative radiation.

Patient Assessment

Patients were evaluated on a regular basis during treatment. The following assessments were performed before each 3-week cycle: physical examination, complete blood count, serum chemistry, and assessment of toxicities. During the initial phase of treatment, complete blood counts were performed twice weekly to determine the nadir values. If the hematological values had not recovered by the time of scheduled treatment, the complete blood count was repeated every week until recovery of leukocyte count to 3.0×10^9/l and platelets to $\geq 100 \times 10^9$/l.

Baseline tumor assessment was performed within 2 weeks of the start of treatment using imaging procedures such as ultrasound, computerized tomography or magnetic resonance imaging. Tumor assessments were repeated after every two cycles of therapy, applying the initially used imaging procedure. World Health Organization (WHO) and NCI-CTC criteria (3.0) were used for the assessment of tumor response and toxicity grading [23, 24].

In addition, time to response (time from start of therapy to first documentation of objective response), duration of response (time from first documentation of objective response to first evidence of progressive disease), time to tumor progression (time from start of therapy to first evidence of progressive disease or last follow-up), and survival (time from start of therapy to death) were measured (intent-to-treat).

Treatment Schedule

Treatment consisted of gemcitabine 1,000 mg/m^2 given as a 30-min infusion on days 1 and 8 and carboplatin AUC 4 given as a 1-hour infusion on day 1 of a 3-week treatment cycle. Treatment was continued until disease progression or the occurrence of unacceptable toxicity.

Dose adjustments were made on the basis of leukocyte and platelet counts on the day of treatment and clinical assessments of nonhematological toxicities. The doses of both drugs were reduced by 25% if the leukocyte count was between 2.5 and 3.0 $\times$ 10^9/l, while the platelet count exceeded 100 $\times$ 10^9/l; if the leukocyte count was less than 2.5 $\times$ 10^9/l *or* the platelet count less than 100 $\times$ 10^9/l, both drugs were omitted. Doses omitted on day 8 were not replaced and the next cycle was given on time as scheduled but at reduced doses. If any toxicity $\geq$grade 3 except nausea/vomiting or alopecia occurred, drug doses were reduced by 50%. If the patient tolerated the dose-modified treatment well, a re-increase of the dose could be attempted in the following cycle. The use of hematopoietic growth factors was allowed in patients with prolonged hematopoietic recovery.

Biometrical Analysis

The primary objective of the study was to determine the objective response rate to the study treatment. Secondary end points included time to progression, survival, and toxicity. Simon's optimal two-stage design [25] was used to ensure that the number of patients exposed to this therapy was minimized should the therapy prove ineffective. The study was planned to distinguish between a clinically uninteresting response rate of 10% (null hypothesis) and a clinically interesting response rate of 30% (alternative hypothesis). With the type I error being 5% and the type II error 10%, 18 patients were to be enrolled during the first step and an additional 17 patients during the second step. If 2 or less responses occurred among the first 18 patients or 6 or less responses in the total population of 35 patients, the treatment had to be judged ineffective and enrolment stopped. If 7 or more responses were observed in the total patient population, the study treatment was judged effective. Assuming a drop-out rate of 10%, enrollment of a total of 39 patients was planned.

The 95% confidence interval (CI) for the overall response rate was determined on the basis of the two-stage design. Time-to-event end points were calculated according to the method of Kaplan and Meier using the STATISTICA software [24, 25]. Patients who received at least one treatment cycle were evaluable for toxicity, and those who had received at least two treatment cycles or those who progressed after the first cycle were evaluable for response (intent-to-treat).

Results

Patient Characteristics

Thirty-nine eligible patients were recruited from 12 German centers. All patients were evaluable for response, toxicity and survival. Median age was 60 years (range 29–77). All patients had previously received chemotherapy, and 33 of them had received up to 5 prior

Table 1. Baseline patient characteristics (n = 39)

Variable	n	%
Age, years		
Median	60	
Range	29–77	
Karnofsky performance status, %		
70–80	7	18
90–100	32	82
Hormone receptor status		
ER or PgR positive	30	77
ER and PgR negative	8	21
Unknown	1	2
HER2 status (IHC)		
0	17	43
1+	7	18
2+	2	5
3+	10	26
Unknown	3	8
Metastatic sites		
1	8	21
2	13	33
≥3	18	46
Sites of metastases		
Liver	30	77
Lung	13	33
Lymph nodes	14	36
Bone	21	54
CNS	5	13
Other sites	23	59
Skin, soft tissue or nodal disease only	2	5
Bone disease only	0	0
Visceral	35	90
Tumor grading		
G1	0	0
G2	17	44
G3	17	44
Unknown	5	13
Prior treatment		
Any CT	39	100
CT for metastatic disease	33	85
Adjuvant CT	24	62
Taxane	26	67
Anthracycline	34	87
Anthracycline + taxane	25	64
Number of prior CT regimens for MBC		
0	6	15
1	14	36
2	8	21
≥3	11	29

CT = Chemotherapy; ER = estrogen receptor; PgR = progesterone receptor; IHC = immunohistochemistry.

chemotherapy regimens for metastatic disease. Twenty-six patients (67%) had previously received anthracyclines and 25 patients (64%) both, an anthracycline- and a taxane-based regimen. Prior endocrine therapy in hormone receptor-positive patients had been applied to 31 patients (80%). Twenty-six patients (67%) had received tamoxifen, and 20 patients had received an aromatase inhibitor (51%). Thirty-five patients presented with visceral metastases (90%) and 31 patients (79.5%) had more than one metastatic site.

Patient characteristics are shown in table 1.

Treatment Delivery

A total of 207 cycles of gemcitabine and carboplatin were delivered. Patients received a median number of 5 cycles (range: 1–12 cycles). Median duration of treatment was 3.8 months (range: 0.5–9.3 months). Dose reductions, delays and omissions occurred in 131 (63%), 65 (31%) and 36 (17%) cycles, respectively.

Response and Survival

All patients were evaluable for efficacy (table 2). One patient achieved a complete response and 11 patients (28.2%) a partial response, for an objective response rate of 30.8% (95% CI: 17.0–47.6%). Overall, disease control rate (objective response plus stable disease) was 61.5% (95% CI: 44.6–76.6%). Disease stabilization was achieved in 12 patients (30.8%), lasting for more than 3 months in 11 (28.2%) and for more than 6 months in 7 patients (17.9%).

A detailed analysis of response with regard to baseline characteristics was undertaken (table 3). Response rate was higher in hormone receptor-positive and HER2-negative patients. Moreover, a higher response rate was observed in patients with one metastatic site only, with less than 3 prior treatment regimens for metastatic disease

Table 2. Efficacy of gemcitabine plus carboplatin

Parameter	Patients	%	95% CI
CR	1	2.6	
PR	11	28.2	
SD	12	30.8	
SD >3 months	11	91.7	
SD >6 months	7	58.3	
PD	12	30.8	
ORR	12	31.0	17–48%
DCR (CR+PR+SD)	24	61.6	

CR = Complete remission; PR = partial remission; SD = stable disease; PD = progressive disease; DCR = disease control rate.

Table 3. Response rates by baseline characteristics

Variable	Total patients	Overall response		
		patients	%	95% CI
Prior CTs for MBC				
0–2 (1st line, 2nd line)	28	11	39.3	21.5–59.4
>2 (beyond 2nd line)	11	1	9.1	0.2–41.3
Metastatic sites				
1	8	5	62.5	24.5–91.5
≥2	31	7	22.6	9.6–41.1
Pretreatment with anthracycline and/or taxane				
With anthracycline	34	11	32.4	17.4–50.5
With taxane	26	7	26.9	11.6–47.8
With both	25	7	28.0	12.1–49.4
Pretreatment without A/T	14	5	35.7	12.8–64.9
Hormone receptor status				
ER *and/or* PgR positive	30	10	33.3	17.3–52.8
ER *and* PgR negative	9	2	22.2	2.8–60.1
HER2 status (IHC, DAKO)				
Positive (3+)	10	2	20.0	2.5–55.6
Negative (0, 1+, 2+, unknown)	29	10	34.5	17.9–54.3

CT = Chemotherapy; A = anthracycline; T = taxane; ER = estrogen receptor; PgR = progesterone receptor; IHC = immunohistochemistry.

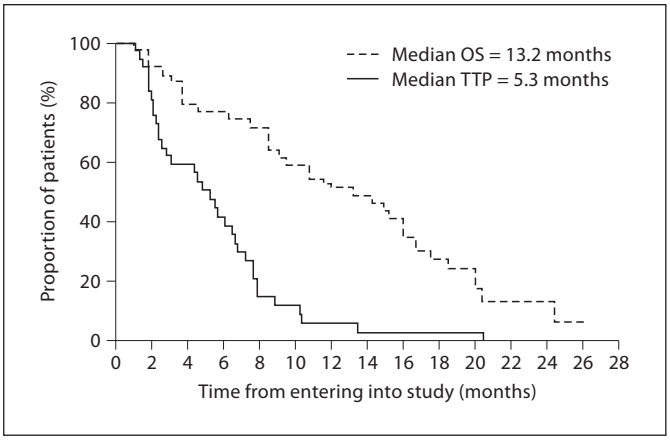

Fig. 1. Time to progression (TTP, ——) and overall survival (OS, – – –).

Table 4. Time-to-event parameters

Parameter	Median months	95% CI months
Remission and progression		
Time to remission	2.6	1.3–5.1
Duration of remission	3.3	3.0–5.8
Duration of stable disease	6.8	5.7–7.9
Time to progression	5.3	2.6–6.7
Survival		
Overall survival	13.2	8.7–16.7

and without prior treatment containing an anthracycline and/or a taxane.

The median time to first observation of an objective response was 2.6 months (95% CI: 1.3–5.1 months). Median duration of response was 3.3 months (95% CI: 3.0–5.8 months), and median time to progression was 5.3 months (95% CI: 2.6–6.7 months). The median overall survival was 13.2 months (95% CI: 8.7–16.7 months). Time to progression and overall survival are shown in figure 1. The time-to-event parameters are listed in table 4.

Toxicity

The predominant hematological toxicity was leukopenia grade 3/4 which occurred in 25 (64%) of the patients and 26% of the applied cycles. Four patients (10%) experienced febrile neutropenia. Growth factor support was applied in 15 patients (38%). Grade 3/4 thrombocytopenia occurred in 19 patients (49%) and 23% of cycles, respectively. Anemia grade 3/4 was less frequent (10% of patients, 3% of cycles).

Nonhematological toxicity was considered mild to moderate. Grade 4 nonhematological toxicity was observed in 8 patients (21%) including elevation of serum transaminases (3% of patients, 0.5% of cycles), elevation of γ-glutamyltransferase (8% of patients, 1.5% of cycles) and dyspnea (8% of patients, 0.5% of cycles). No grade 4 neurotoxicity and nephrotoxicity were observed. Neurotoxicity grade 1 or 2 was observed in 12 patients (31%),

Table 5. Toxicities (number and % of patients)

	Evaluable patients	WHO grade							
		1		2		3		4	
		n	%	n	%	n	%	n	%
Hematological toxicity									
Leukopenia	39	1	3	12	31	23	59	2	5
Febrile neutropenia	39	0	0	2	5	1	3	1	3
Thrombocytopenia	39	9	23	8	21	10	26	9	23
Anemia	39	10	26	25	64	4	10	0	0
Nonhematological toxicity									
Alopecia	39	6	15	16	41	3	8	0	0
Nausea/vomiting	39	19	49	16	41	0	0	0	0
Asthenia	39	15	38	6	15	0	0	0	0
Neurotoxicity	39	8	21	4	10	0	0	0	0
Nephrotoxicity	39	7	18	1	3	1	3	0	0
Alkaline phosphatase	39	16	41	4	10	4	10	0	0
AST	39	21	54	12	31	2	5	1	3
ALT	39	16	41	11	28	5	13	0	0
Bilirubin	39	2	5	2	5	4	10	0	0

Table 6. Overview of clinical trials regarding treatment of MBC patients with gemcitabine and platinum salts either as single agents or in combination

Reference	n	Regimen	OR, %	TTP, months	OS, months
1st-line gemcitabine (GEM)					
Blackstein et al. [2]	39	GEM	73.1	5.1	21.1
2nd-line gemcitabine (GEM)					
Brodowicz et al. [3]	25	GEM 2nd-line (n = 9);	22	5.1	12.6
		3rd-line (n = 16)	12	3.5	7.5
Spielmann et al. [5]	47	GEM	29	8.1	n.a.
Carmichael et al. [34]	40	GEM 1st-/2nd-line	25	1.9	11
Smorenburg et al. [35]	23	GEM	0	1.9	7.8
1st-line carboplatin (CBDA)					
Kolaric and Vukas [11]	20	carboplatin	20	n.a.	n.a.
2nd-line carboplatin (CBDA)					
Martin et al. [12, 13]	34	carboplatin	35	8	n.a.
O'Brien et al. [14]	40	carboplatin	8	4.5	n.a.
		1st-line (n = 13)	33		
		2nd-line (n = 27)			
1st-line GEM/cisplatin					
Mohran [9]	25	GEM/cisplatin	54.5	n.a.	14.8
Fuentes et al. [10]	46	GEM/cisplatin	81	14.9	27.9
Alauddin and Shaharyar [36]	30	GEM/cisplatin	76.7	n.a.	n.a.
2nd-line GEM/cisplatin or carboplatin					
Burch et al. [37]	58	GEM/cisplatin	29 (high dose)	7.7	16.9
		(2 dose levels)	32 (low dose)	6.5	13.5
Seo et al. [6]	30	GEM/cisplatin	30	7	15
Heinemann et al. [7]	38	GEM/cisplatin	40	6	13.5
Chitapanarux et al. [8]	30	GEM/cisplatin	52	n.a.	n.a.
Moura et al. [38]	74	GEM/cisplatin	30	7.7	18.3
Nasr et al. [21]	30	CEM/carboplatin	30	5.1	n.a.
Nagourney et al. [20]	12	GEM/carboplatin	50	5	n.a.
Latini et al. [19]	13	GEM/carboplatin	69.2	n.a.	n.a.
Silva et al. [33]	19	GEM/carboplatin	21.5	n.a.	7.5

TTP = Time to progression; OS = overall survival; GEM = gemcitabine; n.a. = not available.

and nephrotoxicity grade 1–2 was documented in 8 patients (21%). Hematological and nonhematological toxicities are shown in table 5.

Discussion

With the increasing use of anthracycline- and taxane-based regimens in the adjuvant and neoadjuvant setting and their established application in the treatment of the advanced and metastatic stages of breast cancer, there is a clear need for non-cross-resistant further-line regimens. While there is no established standard of chemotherapy for anthracycline- and taxane-pretreated patients, capecitabine has become a widely accepted agent in this treatment setting. In phase II and III trials response rates in the range of 26–52% and time to progression of 3.6–8.9 months were reported [26–30].

The preclinical rationale for a combination of gemcitabine with a platinum analog is supported by the synergistic interaction of both agents [17, 18, 31]. Several clinical studies performed with various schedules have demonstrated that the combination of gemcitabine and cisplatin is highly active not only in first-line treatment, but also in patients previously exposed to anthracyclines and/or taxanes (table 6). While a formal comparison of carboplatin and cisplatin has never been performed in MBC, the available evidence suggests a better tolerability of carboplatin [32]. Due to its lower emetogenic and nephrotoxic potential carboplatin may be specifically preferred in intensively pretreated patients. Moreover, time-consuming hydration regimens can be avoided with carboplatin.

The present study evaluated a 3-week regimen, where gemcitabine was applied on days 1 and 8, while carboplatin was given on day 1. Most patients had undergone previous treatment with anthracyclines (67%) and/or taxanes (64%). The efficacy of gemcitabine plus carboplatin (overall response rate 31%, 95% CI: 17–48%) reached the predefined endpoint of a clinically relevant activity. The median duration of most responses and disease stabilizations was 3.3 and 6.8 months, respectively. The median time to progression was 5.3 months resulting in a median overall survival of 13.2 months.

Comparable results have also been reported by Nasr et al. [21] who investigated a schedule where gemcitabine (1,000 mg/m^2, days 1 + 8) and a greater dose of carboplatin (AUC 5 on day 1) were applied in a 3-week regimen. The combination was given to 30 MBC patients as a second-line treatment. The overall response rate was 30% and median time to progression was 4.8 months. Main grade 3/4 hematological toxicities were neutropenia in 50% of patients (20% of whom had febrile neutropenia), anemia in 26.6% and thrombocytopenia in 30% of patients.

The same schedule was evaluated by Silva et al. [33] in 19 comparably pretreated MBC patients yielding an overall response rate of 21.5% and a median overall survival of 7.5 months. Main hematological toxicities included anemia (21% of patients), neutropenia (21%), and thrombocytopenia in 5% of patients.

Nagourney et al. [20] reported a 'repeating doublet' regimen, where gemcitabine (800 mg/m^2) and carboplatin (AUC 2) were both applied on days 1 and 8 of a 3-week regimen. Ten evaluable patients with first or second recurrence of MBC had received the schedule with an overall response rate of 50% (including 1 complete response) and a median time to progression of 5 months (range 2–20 months). Most commonly reported grade 3 and 4 side effects were neutropenia (60% of patients) and thrombocytopenia (40% of patients).

The treatment-associated toxicity profile in our study was generally acceptable. Hematological toxicity (grade 3 and 4), mainly leukopenia and thrombocytopenia, occurred in 26 and 23% of the applied cycles, respectively. The rate of febrile neutropenia was low (6% of patients) as compared to an incidence of 20% in the study by Nasr et al. [21]. As a consequence, a median of five cycles could be administered without significant delays or dose reductions. Nevertheless, 38% of the patients required hematopoietic growth factor support. This is in part explained by the intensive pretreatment observed in most of the patients. Thus, for the considerable incidence of severe thrombocytopenia it would be reasonable to consider starting gemcitabine at the lower dose level of 800 mg/m^2. Symptomatic adverse events such as nausea/vomiting or asthenia were generally mild to moderate. There was no patient who developed renal dysfunction ($\geq$grade 2).

Certainly, an optimal regimen of gemcitabine/carboplatin for intensively pretreated MBC patients has not been determined in a comparative fashion. It appears, however, that the application of carboplatin on day 1 may be preferred to the repeating doublet regimen since the latter was associated with a higher incidence of hematological toxicity (neutropenia 26 vs. 60%, thrombocytopenia 23 vs. 40%).

In conclusion, the combination of gemcitabine plus carboplatin is a generally well-tolerated and effective regimen that provided sustained disease control in intensively pretreated breast cancer patients. Specifically after previous exposure to anthracyclines and/or the taxanes, this regimen can be considered as an active treatment option which offers a favorable balance between efficacy and tolerability.

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