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ORIGINAL ARTICLE

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High efficacy of gemcitabine and cisplatin in patients with predominantly anthracycline- and taxane-pretreated metastatic breast cancer

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Abstract *Background*: Effective and tolerable regimens are sought specifically in patients who have been pretreated with anthracyclines and taxanes. Gemcitabine and cisplatin demonstrated synergistic activity in vitro and provides a new mechanism of drug interaction. *Patients and methods*: Previously treated patients with metastatic breast cancer (MBC) were enrolled in a multicentre phase II study. Treatment consisted of gemcitabine (750 mg/m^2) and cisplatin (30 mg/m^2) given on day 1 and 8 every 3 weeks. *Results*: Thirty-eight patients were recruited, all of whom had previously received chemotherapy (35 pretreated with taxanes, 33 pretreated with anthracyclines). A median of 5 cycles of the study treatment was delivered. There were 2 complete and 13 partial responses, for an overall response rate of 40% (95% confidence interval: 23–56%). Thirteen patients (35%) had stable disease. Tumour response appeared independent of previously applied chemotherapy. Median time-to-progression was 6 months and median overall survival was 13.5 months. Main toxicities were leucopenia and thrombocytopenia (grade 3/4 in 26 and 16% of cycles, respectively). Non-haematological toxicity was rarely severe. *Conclusions*: Combination chemotherapy with gemcitabine and cisplatin given on 2 out of 3 weeks is well tolerated and active in heavily pretreated patients with MBC, even after prior exposure to anthracyclines and taxanes.

Keywords Gemcitabine · Cisplatin · Anthracycline resistance · Metastatic breast cancer

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Introduction

Metastatic breast cancer (MBC) treatment is characterized by the availability of multiple treatment options made possible by active single agents and their combinations, the effectivity of which is not limited to first- and second-line settings. Strategies are confounded by the increasing exposure of patients to chemotherapy, including anthracycline- and taxane-based regimen in the neoadjuvant and adjuvant setting.

Two general strategies are apparent and should be followed: (1) improving treatment efficacy by exploring new drugs and drug combinations, and (2) ensuring that efficacy is improved at the lowest cost to quality of life.

Gemcitabine monotherapy has produced overall response rates up to 37% in the first-line setting and 26 or 13% in the second- or third-line setting [3–9]. In studies limited to second- or third-line therapy after anthracycline and/or taxane exposure, response rates have reached 29% and median time-to-progression has varied from 2 to 6 months [3–9]. Various combinations of gemcitabine with other effective agents have resulted in high response rates.

Cisplatin, a bifunctional DNA cross-linking agent, has shown marked activity in various solid tumours, but has not been established in MBC therapy. A consistently low response rate of 0–15.4% observed in five studies is contrasted by high first-line activity reported in two trials (47 and 54%) [11]. It appears that cisplatin

resistance 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 the rationale for the combination of both agents. Synergistic cytotoxicity observed in vitro clearly relates to this drug interaction [15, 21, 22]. Exposure to cisplatin causes an activation of DNA repair polymerases and thereby enhances the incorporation of gemcitabine triphosphates into DNA repair patches [15, 23]. Once integrated into DNA, gemcitabine is not readily recognized and excised by proofreading exonucleases and may trigger signalling pathways leading to apoptosis [1]. Several considerations support the use of gemcitabine and cisplatin in salvage therapy and make it a particularly attractive treatment option for MBC: (1) This combination has shown additive or synergistic activity in vitro, which was most pronounced in cisplatin-resistant cell lines and was found to be due to an increased formation and an impaired repair of platinum–DNA adducts [15, 21]. (2) Gemcitabine and cisplatin are usually not included into adjuvant or neoadjuvant chemotherapy; therefore, resistance to either drug is unlikely to occur. (3) There is minimal overlapping toxicity for gemcitabine and cisplatin, suggesting acceptable toxicity even in intensively pretreated patients. (4) Finally, the addition of trastuzumab to gemcitabine/cisplatin might form an effective triplet combination, and thus may offer another treatment option after anthracycline and taxane pretreatment [14].

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

Patients and methods

Patient population

Thirty-eight patients with histologically confirmed MBC were recruited on 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 to have at least one bidimensionally measurable lesion outside a previous radiation port. Other eligibility criteria included age from 18 to 70 years, Karnofsky performance status ≥70%, minimal life expectancy of 12 weeks, and adequate haematological, renal, cardiac, and hepatic function (leukocyte count $\geq 3.0 \times 10^9$/l or absolute neutrophil count (ANC) $\geq 2 \times 10^9$/l; platelet count $\geq 100 \times 10^9$/l; haemoglobin ≥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; and 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, if they had bone metastases alone, 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.

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 haematological 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 tumour assessment was performed within 2 weeks of start of treatment using imaging procedures such as ultrasound, computerized tomography or magnetic resonance imaging. Tumour assessments were repeated after every two courses of therapy, applying the initially used imaging procedure.

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-tumour 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). World Health Organization (WHO) criteria were used for the assessment of tumour response and toxicity grading [2, 12].

Treatment schedule

Treatment consisted of gemcitabine 750 mg/m^2 given as a 30-min infusion and cisplatin 30 mg/m^2 given as a 1 h infusion on day 1 and 8 of a 3-week treatment cycle. Before infusion of cisplatin, patients received hydration with 1 l/m^2 over 2 h or oral application of 2–3 l mineral water over 8 h. Immediately before cisplatin, patients received intravenous furosemide 20 mg. Posthydration was performed 2–24 h after cisplatin administration using an oral application of at least 1 l/m^2 . 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 non-haematological toxicities. The doses of both drugs were reduced by 25% if the leukocyte count was between 2.5 and 3.0×10^9/l, while the platelet count exceeded 100×10^9/l; if the leukocyte count was less than 2.5×10^9/l or the platelet count less than 100×10^9/l, the doses of both drugs were omitted. Omitted day-8 doses were not replaced, but the next cycle was given as planned but at reduced doses. If any toxicity ≥ grade 3 except nausea/vomiting or alopecia occurred, drug doses were reduced by 50%. If the patient tolerated the dose-modified treatment well, a reincrease of dosage could be attempted in the following cycle. If the creatinine clearance fell below 60 ml/min, cisplatin administration was discontinued, and in the case of any grade 4 non-haematological toxicity the study chemotherapy was discontinued.

The use of haematopoietic growth factors was allowed in patients with protracted myelosuppression. Administration of other cytotoxic, immune or hormonal agents or radiation therapy was not permitted during the study, with the exception of contraceptives, steroids given as analgetic or antiemetic treatment, or local palliative radiation.

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 was used to ensure that the number of patients exposed to this therapy was minimized, should the therapy prove ineffective [18]. 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 stage and an additional 17 patients during the second stage. 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 dropout rate of 10%, it was planned to enrol a total of 39 patients.

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 [12, 18]. Patients who received at least one treatment cycle were evaluable for toxicity, and those receiving at least two treatment cycles or those who progressed after the first cycle were evaluable for response.

Results

Patient characteristics

Thirty-eight eligible patients were recruited from 11 German centres. All patients were evaluable for response, toxicity, and survival. Patient characteristics are shown in Table 1. Median age was 58 years (range: 41–69). All patients had previously received chemotherapy, and 31 of them had received up to 4 prior chemotherapy regimens for metastatic disease. Thirty-three patients (87%) had previously received anthracyclines, and 30 patients (79%) both an anthracycline- and taxane-based regimen. More than half of the patients were considered either resistant (8 patients, 21%) or refractory (16 patients, 42%) to anthracyclines. Thirty-three patients (87%) had visceral disease, and 22 patients (58%) had more than one metastatic site.

Treatment delivery

A total of 188 cycles of gemcitabine and cisplatin were delivered. Patients received a median number of 5 cycles (range: 1–11). Median duration of treatment was 3.9 months (range: 0.3–7.7). Dose reductions, delays, and omissions occurred in 29 (15%), 28 (15%), and 14 (7%) cycles, respectively. The reasons for dose modifications or omissions included leucopenia (24 cycles), anaemia (21 cycles), thrombocytopenia (15 cycles), nausea and vomiting (7 cycles), and others including personal reasons (4 cycles). Most patients could receive full doses of both drugs during cycles 1–3.

Response and survival

Two patients (5%) achieved a complete response and 13 patients (35%) a partial response, for an objective response rate of 40% (95% CI: 23–56%). Thirteen additional patients (35%) had stable disease, and tumour progression occurred in ten patients (27%). Overall, disease control (objective response plus stable disease) was obtained in 78% of patients (95% CI: 59–88%).

A descriptive analysis of response by several baseline characteristics was performed (Table 2). Response rate was higher in younger (< 55 vs. ≥55 years) and hormone receptor positive patients. No clear relationship was observed between the response to gemcitabine/cisplatin and the number of metastatic sites, tumour grading, the number of pretreatment regimens, and anthracycline sensitivity.

The median time-to-first observation of an objective response was 1.7 months (0.2–5.6). Median duration of response was 5.0 months (range: 0.9–17.5), and median time-to-progression was 6.0 months (range:

Table 1 Baseline patient characteristics

Variable	Patients (n = 38)	
	No.	%
Age (years)		
Median	58	
Range	41–69	
Karnofsky performance status (%)		
70–80	6	16
90–100	32	84
Menopausal status		
Premenopausal	6	16
Postmenopausal	32	84
Hormone receptor status		
ER or PgR positive	25	66
ER and PgR negative	11	29
Unknown	2	5
HER2 status		
0	13	34
1+	4	11
2+	1	3
3+	3	8
Unknown	17	45
No. of metastatic sites		
1	16	42
2	15	39
3 or 4	7	18
Sites of metastases		
Liver	27	71
Lung	11	29
Lymph nodes	12	32
Bone	9	24
Other sites	10	26
Visceral disease	33	87
Skin, soft tissue or nodal disease only	5	13
Bone disease only	0	0
Tumour grading		
G1	5	13
G2	13	34
G3	16	42
Unknown	4	11
Prior treatment		
Any CT	38	100
Palliative CT	31	82
Adjuvant CT	24	63
Adjuvant and palliative CT	17	39
Taxane	35	92
Anthracycline	33	87
Anthracycline + taxane	30	79
No. of prior CT regimens for metastatic disease		
0	7	18
1	12	32
2	9	24
3 or 4	10	26
Sensitivity to prior anthracyclines		
Not exposed	5	13
Sensitive	9	24
Resistant[a]	8	21
Refractory[b]	16	42
Time from diagnosis to start of study CT (months)		
Median	40.5	
Range	4–108	

Abbreviations: CT, chemotherapy; ER, estrogen receptor; PgR, progesterone receptor

[a] Patients were considered resistant if they relapsed within 12 months after completion of anthracycline-based adjuvant chemotherapy, or if they initially responded to anthracycline-based chemotherapy for metastatic disease but progression occurred while still on therapy

[b] Patients were considered refractory if they never achieved an objective response to anthracycline-based palliative chemotherapy and progressed while on therapy

Table 2 Response rates by baseline characteristics

Variable	Total no. of patients	Overall response		
		No. of patients	%	95% CI
Age (years)				
< 55	16	9	56	29–84
55–69	22	6	27	7–47
No. of prior CTs for metastatic disease				
0	7	3	43	7–92
1	12	5	42	9–74
2	9	2	22	12–56
≥3	10	5	50	12–88
No. of metastatic sites				
1	16	6	38	11—64
≥2	22	9	41	19–63
Anthracycline sensitivity				
Sensitive or not exposed	14	5	36	7—64
Resistant or refractory	24	10	42	20–63
Hormone receptor status				
Positive	25	12	48	27–69
Negative	11	3	27	4—59
Grading				
G1	5	2	40	3—100
G2	13	3	23	3–50
G3	16	9	56	29–84

Abbreviation: CT, chemotherapy

1.1–23.8+). The median overall survival amounts to 13.5 months (range: 1.1–39+). The time-to-progression and the overall survival curve are shown in Fig. 1, and the time-to-event parameters are listed in Table 3.

Toxicity

Haematological and non-haematological toxicities are shown in Table 4. The predominant haematological toxicity was leucopenia that reached WHO grade 3 in 19 (50%) patients and 23% of cycles and grade 4 in 5 (13%) patients and 3% of cycles. There were 2 patients (5%) who developed febrile neutropenia. Growth factor support due to grade 4 or febrile neutropenia was necessary in 4 patients (11%). Grade 3/4 thrombocytopenia occurred in 14 (37%) patients and 16% of cycles. Anaemia grade 3/4 was less frequent and occurred in 13% of patients and 3% of cycles.

Non-haematological toxicity was mild to moderate in the majority of patients. Patients with no hair loss at treatment start generally did not experience alopecia grade >1. No grade 4 non-haematological toxicity was

Table 3 Time-to-event parameters

Parameter	Median (range) (months)
Time-to-response	1.7 (0.2–5.6)
Duration of response	5.0 (0.9–17.5)
Time-to-progression	6.0 (1.1–23.8)
Overall survival	13.5 (1.1–39.2+)

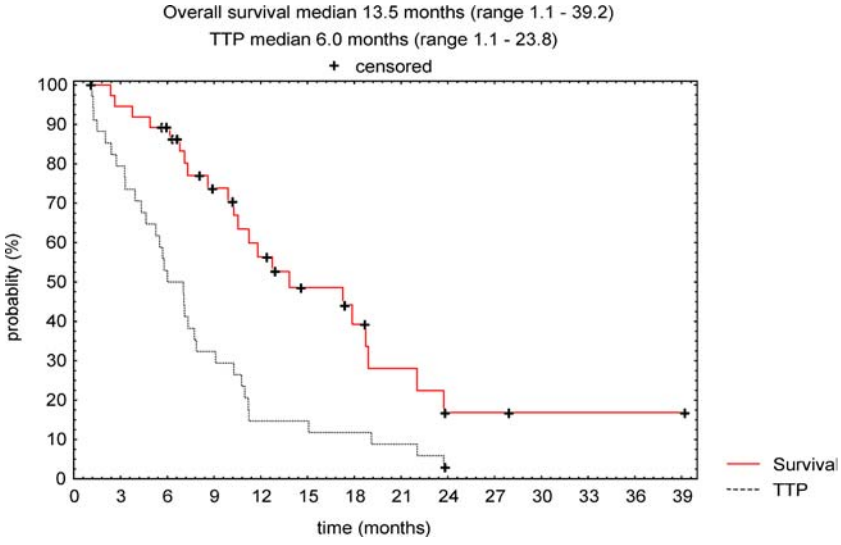

Fig. 1 Time-to-progression and overall survival

reported. Grade 3 toxicities included nausea and vomiting (5% of patients, 4% of cycles), asthenia (5% of patients, 2% of cycles), elevations of serum alkaline phosphatase (3% of patients, 1% of cycles), and serum transaminases (14% of patients, 5% of cycles). Neurotoxicity grade 1 or 2 was observed in 7 patients (18%).

Discussion

With the increasing use of anthracycline- and taxane-based regimen in the adjuvant and neoadjuvant settings and their established application in the treatment of the advanced and metastatic stages of breast cancer, there is a need for non-cross-resistant regimens.

The efficacy, in particular, response rate and median time-to-progression, reached by single-agent gemcitabine in second- or third-line therapy after anthracycline and/or taxane exposure is quite unsatisfactory (response rates 29%, median TTP 2–6 months), thus combination therapy is required [3, 4, 6, 17, 19, 20]. The rationale for a gemcitabine-based combination treatment is supported by its unique mechanism of action allowing synergistic cytotoxic interaction with cisplatin. Gemcitabine acts as an effective inhibitor of DNA repair and thereby may overcome drug resistance induced by an upregulation of DNA repair [1, 15, 21, 23].

Several small studies with various schedules have demonstrated that the gemcitabine–cisplatin combination is highly active and generally well tolerated in previously treated patients with MBC. In six studies performed in moderate to intensively pretreated patients, which used lower doses of cisplatin given repeatedly or once during 3- or 4-week cycles, demonstrated a median overall response rate of 39% (range: 29–50%) [5, 7–10, 13]. The study presented here is the first that used a day-1 and day-8 schedule as described by Nagourney et al. consistently from the beginning.

Table 4 Toxicities (number and % of patients)

	No. of evaluable patients	WHO grade							
		1		2		3		4	
		No.	%	No.	%	No.	%	No.	%
Haematological toxicity									
Leucopoenia	38	3	8	10	26	19	50	5	13
Febrile neutropenia	38	–	–	–	–	–	–	2	5
Thrombocytopenia	38	13	34	8	21	12	32	2	5
Anaemia	38	17	45	13	34	2	5	3	8
Non-haematological toxicity									
Alopecia	38	2	5	7	18	4	11	0	0
Nausea/vomiting	38	14	37	8	21	2	5	0	0
Asthenia	38	10	26	2	5	2	5	0	0
Neurotoxicity	38	6	16	1	3	0	0	0	0
Alkaline phosphatase	35	6	17	2	6	1	3	0	0
AST/ALT	35	2	6	4	11	5	14	0	0
Bilirubin	35	0	0	3	9	0	0	0	0
Creatinine	35	9	26	0	0	0	0	0	0

In view of the heavy pretreatment of many patients, the efficacy of chemotherapy with gemcitabine and cisplatin in the present study was quite satisfactory, with an overall response rate of 40% (95% CI: 23–56%) including 5% complete responses. An additional 35% of the patients had stable disease. It appears particularly noteworthy that the response rate was not decreased in patients with anthracycline-resistant or refractory disease compared with those who were sensitive or not exposed to anthracyclines (42 vs. 36%). Remarkably, even 5 of 10 patients who had received 3 or 4 prior chemotherapy regimens for metastatic disease achieved a response. Most responses and disease stabilizations were durable, with a median response duration of 5 months and median time-to-progression of 6 months leading to a median overall survival of 13.5 months. These results are in the range of those obtained with other gemcitabine–cisplatin schedules and compare favourably with other combination regimens commonly used in anthracycline-pretreated patients with MBC. Burch et al. administered gemcitabine 1,000 mg/m^2 and cisplatin 25 mg/m^2 on day 1, 8, and 15 of a 4-week cycle [5]. The combination was given to 21 patients previously treated with anthracyclines and/or taxanes. The overall response rate was 29% and median duration of response amounts to 7.1 months. The same schedule was evaluated by Chaudry et al. in 28 patients with similar pretreatment, resulting in an overall response rate of 39% and a median response duration of 4.8 months [7]. Galvez et al. used another schedule, with gemcitabine 1,200 mg/m^2 given on day 1, 8, and 15, and cisplatin 50 mg/m^2 on day 1 every 4 weeks [10]. Forty-one patients with prior exposure to anthracyclines were treated with this schedule as second-line therapy, with an overall response rate of 49%, and a median response duration of 10.6 months. Excellent results were obtained in a small study with gemcitabine 1,000 mg/m^2 applied on day 1 and 8, and cisplatin 75 mg/m^2 on day 2 every 4 weeks [8]. Ten of 16 patients (63%) obtained a response, and the median TTP was 11.2 months. The patients in this study had previously received one or two chemotherapy regimens, but prior exposure to anthracyclines or taxanes was not reported. The perspective of the gemcitabine–cisplatin combination is provided by a single trial performed in the first-line treatment of MBC, where an overall response rate of 80% was reported applying gemcitabine 1,200 mg/m^2 on day 1 and 8 and cisplatin 75 mg/m^2 on day 1 of a 3-week cycle [16].

Although severe haematological toxicity (grades 3 and 4), mainly leucopenia and thrombocytopenia, was observed in 26 and 13% of cycles, respectively, the treatment-associated profile of side effects was generally acceptable. The rate of severe febrile neutropenia was low. As a consequence, a median of five cycles could be administered without significant delays or dose reductions. Additionally, a minority of the patients required the support of haematopoietic growth factors (n = 4). This is particularly noteworthy as the majority of our patients had received two or more prior chemotherapy regimens including a taxane, and 33 had previously been treated with an anthracycline. Symptomatic adverse events such as nausea/vomiting or asthenia were generally mild to moderate. There was no patient who developed renal dysfunction.

At present, an optimal regimen for the treatment of MBC has not been determined in a comparative fashion. To optimize synergy, it was suggested to administer ‘repeating doublets‘ of drugs such as the application used in the Nagourney regimen in which both drugs were given on day 1 and 8 [13]. If outpatient use is preferred, the lower weekly cisplatin dose (30 mg/m^2) in combination with gemcitabine 750 mg/m^2 given on day 1 and 8 every 3 weeks proved to be a well tolerated and effective regimen that provided sustained disease control in intensively pretreated breast cancer patients. Specifically after previous exposure to anthracyclines and/or taxanes, this regimen should be considered as an active treatment option. The schedule appears to offer a favourable balance between efficacy and tolerability. Further investigation of the schedule in randomized trials is mandatory.

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