Review

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Role of Gemcitabine in the Treatment of Advanced and Metastatic Breast Cancer

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Key Words
Breast cancer · Combination therapy · Gemcitabine · Single agent

Abstract
Gemcitabine is an antimetabolite drug with proven antitumor activity and tolerability in metastatic breast cancer. In a total of nine studies, gemcitabine monotherapy has reached response rates of up to 37% in the first-line setting, 26% in the second-line setting, and 18% or better in the third-line setting. Gemcitabine is an excellent choice for combination therapy by its unique mechanism of action and favorable toxicity profile, thus limiting the risk of pretreatment-related drug resistance and overlapping toxicity, and by its potential for synergistic interaction with some combination partners as indicated in preclinical studies. Numerous phase II clinical studies have combined gemcitabine with other active agents such as the taxanes, vinorelbine, vindesine, cisplatin, 5-fluorouracil, as well as anthracyclines across various regimens and conditions of pretreatment. Most of these two-drug combinations have consistently demonstrated higher efficacy than either single agent, particularly in pretreated patients. Even higher efficacy has been obtained with triple-drug regimens including gemcitabine, anthracyclines (epirubicin or doxorubicin), and paclitaxel; these regimens have yielded overall response rates of 58–92% as first-line treatment. In view of these results, gemcitabine may be regarded as a valuable alternative to the palliative treatment of metastatic breast cancer, and an excellent option for the development of effective combination treatment not only in first-line therapy, but also for intensively pretreated patients previously exposed to anthracyclines and/or the taxanes.

Introduction

Metastatic breast cancer treatment is characterized by the availability of multiple treatment options made possible by active single agents and their combinations, the effectiveness of which is not limited to first- and second-line settings.

Single-agent therapy in chemonaive patients has achieved overall response rates of 25–55%, which may be improved further to 35–80% with combination therapy [1]. Median durations of response have been in the range of 6–12 months in most studies. In randomized phase III trials, front-line monotherapy has attained median progression-free survival times of 4–8 months and median survival times of 14–22 months [2–5]. As second-line treatment, single agents have produced response rates of 20–40% and response durations of 2–8 months [1].

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Despite progress in the development and understanding of new drugs, clearly defined steps toward improved survival in patients with advanced breast cancer have not been delineated recently. Strategies are confounded by the increasing exposure of patients to chemotherapy in the adjuvant setting. Nevertheless, 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 with the lowest cost to quality of life.

Gemcitabine (2′2′-difluorodeoxycytidine, dFdC) is a novel nucleoside antimetabolite that has proven systemic and preclinical antitumor activity in a variety of human solid tumors, including pancreatic, non-small-cell lung, bladder, ovarian, as well as breast tumors [6–8]. The parent compound is phosphorylated intracellularly by deoxycytidine kinase to the active metabolites, gemcitabine diphosphate, and triphosphate [9]. Gemcitabine triphosphate competes with deoxycytidine triphosphate (dCTP) for incorporation into DNA as a fraudulent base, which results in masked chain termination and inhibition of further DNA synthesis. Gemcitabine diphosphate inhibits ribonucleotide reductase, an enzyme responsible for catalyzing dCTP. The subsequent decrease in dCTP potentiates the incorporation of gemcitabine triphosphate into DNA, and enhances phosphorylation of gemcitabine since there is less dCTP to inhibit deoxycytidine kinase [10, 11]. These self-potentiating mechanisms prolong the retention of active gemcitabine in tumor cells.

Among the multitude of available agents, gemcitabine stands out because of its good tolerability and side-effect profile [12]. The mild toxicity of gemcitabine certainly favors its combination with other antitumor drugs. In addition, the novel mechanism of action of this agent [11] reduces the possibility of pretreatment-associated drug resistance.

While gemcitabine has already demonstrated clinical efficacy as a single agent in breast cancer [13–21], knowledge regarding its treatment profile in combination therapy against this tumor is only recently emerging. On this basis, this review has evaluated the clinical applicability and efficacy of gemcitabine-based combination therapy in metastatic breast cancer.

Methods

The MEDLINE database was searched for publications related to the use of gemcitabine in breast cancer [22]. In addition to full publications, abstracts presented at the meetings of the American Society of Clinical Oncology (ASCO), the European Cancer Conference (ECCO), and the San Antonio Breast Cancer Meeting were also included. The present review considered only those publications that included at least 19 evaluable patients. Phase I data were not included (except in cases where phase II results were not available), and phase III studies have not yet been reported. Because survival data are typically not reported in phase II trials, we did not include these data in this review; however, this review did include time to disease progression whenever reported, as this endpoint is relevant to these studies.

Results

Single-Agent Gemcitabine

Nine studies are available that provide an initial assessment of the single-agent activity and tolerability of gemcitabine in advanced breast cancer [13–21] (table 1). Comparability among the studies is limited by different gemcitabine regimens and conditions of pretreatment. The most frequently applied regimens were doses of 1,000 or 1,200 mg/m^2 administered over 4-week cycles.

Gemcitabine monotherapy has produced overall response rates of up to 37% in the first-line setting [13–15], 26% in the second-line setting [15, 17], and 13% in the third-line setting [17]. In studies limited to second- or third-line therapy after anthracycline and/or taxane exposure, response rates have reached 29% [16, 17, 19]. Median time to progression has varied from 2 to 6 months [13–17, 20, 21].

The considerable difference between response rates produced by the first-line studies of Blackstein and Possinger (37 vs. 14%) remains unclear [13, 14]. The lower gemcitabine dose intensity in the Possinger study (994 mg/m^2) compared to that of the Blackstein study (1,053 mg/m^2) can hardly be claimed as a reason for the lower treatment activity, as the remission rate in the Carmichael study, which reported an even lower dose intensity (775 mg/m^2), was nearly twice as high (25%). Moreover, the ratios of patients with estrogen receptor positivity and prior adjuvant treatment were lower, and therefore more favorable, in the Possinger study. It should be pointed out, however, that the percentage of patients achieving stable disease was comparatively higher in the Possinger study (57 vs. 49%). Accordingly, the inhibition of tumor progression (stable disease + overall response) did not differ greatly between the studies (57 + 14% for Possinger and 49 + 37% for Blackstein).

In one study in which all patients had failed both anthracycline- and taxane-based chemotherapy, there were no responders, although 6 of the 21 evaluable patients achieved stable disease [21]. The heavy pretreat-

Table 1. Gemcitabine monotherapy

Reference (first author)	N/Resp eval	Prior chemotherapy	Study dose mg/m^2	Median TTP, months	ORR, %	WHO grade 3 or 4 toxicity[a], n or % of patients
Blackstein [13]	39/35	1st-line 39 pts Adjuvant 19 pts	1,200 d1, 8, 15 q 4 wks	5.1	37 (median RD = 8.8 mos)	*G3:* neutropenia (9), thrombocytopenia (2), ALT (2), cutaneous (1), nausea/vomiting (4); *G4:* pulmonary (1), infection (1)
Possinger [14]	42/42	1st-line 42 pts Adjuvant 10 pts	1,000 d1, 8, 15 q 4 wks	3.8	14 (median RD = 5.6)	*G3/4:* nausea/vomiting (6), ALP (1), ALT (8), neutropenia (8), thrombocytopenia (2); *G3 only:* ALP (1), AST (2)
Carmichael [15]	44/40	1st-line 14 pts 2nd-line 19 pts Anthracyclines 17 pts Adjuvant 7 pts	800 d1, 8, 15 q 4 wks	2.1[b]	25.0 (median RD = 13.5 mos) 1st-line: 36 (5/14) 2nd-line: 26 (5/19)	*G3/4:* neutropenia (30%), leukopenia (9%); anemia and thrombocytopenia mininal; AST (9%), nausea/vomiting (27%); *G4 only:* infection (2%); *G3 only:* allergic, rash, cardiac function, alopecia, altered consiousness (2% for each)
Valerio [16]	26/22	2nd- or 3rd-line 26 pts Anthracycline, taxane	1,000 d1, 8, 15 q 4 wks	NA	23	No grade 3 or 4 toxicity was reported; main toxicities were influenza-like syndrome with fever (10) and fatigue (8)
Brodowicz [17]	25/25	2nd-line 9 pts 3rd-line 16 pts Anthracyclines 25 pts Taxanes 6 pts	1,250 d1, 8, 15 q 4 wks	3.6 2nd-line: 5.1 3rd-line: 3.5	16 2nd-line: 22 (2/9) 3rd-line: 13 (2/16)	*G3:* thrombocytopenia (1) *G4:* thrombocytopenia (4)
Gerson [18]	19/19	1st-line 2 pts 2nd-line 6 pts 3rd-line 6 pts >3rd-line 5 pts	1,250 d1, 8, 15 q 4 wks	NA	42 (median RD = 8.5 mos)	Hematologic side effects (9; grade not reported), grade 2/3 thrombocytopenia (5); nausea, vomiting, dysuria, alopecia (2 each; grade not reported)
Spielmann [19]	47/41	2nd-line 32 pts 3rd-line 15 pts (≥1 anthracycline- or anthracenedione-based CT) Adjuvant 11 pts	1,200 d1, 8, 15 q 4 wks	NA	29 (median RD = 8.1 mos)	*G3:* neutropenia (13), thrombocytopenia (3), nausea/vomiting (4), cutaneous (1); *G4:* neutropenia (1)
Schmid [20]	20/20	1st-line 4 pts 2nd-line 5 pts ≥3rd-line 11 pts Adjuvant 10 pts Anthracyclines 15 pts	250, 6-hour infusion, d1, 8, 15 q 4 wks	6.3	25 ≥3rd-line: 18 (2/11)	*G3 only:* leukopenia (4% of cycles); AST, ALT (10% of cycles for each); GGT (8% of cycles), nausea/vomiting (4% of cycles), alopecia (3% of cycles)
Smorenburg [21]	23/21	2nd-line 3 pts ≥3rd-line 20 pts Failed anthracycline- and taxane-based CT Adjuvant 11 pts	1,200 d1, 8, 15 q 4 wks	1.9	0	*G3:* neutropenia (3), thrombocytopenia (1), nausea/vomiting (3), cutaneous (2), AST (3), ALT (5); *G4:* neutropenia (1)

Resp eval = Response evaluable; TTP = time to progression; ORR = overall response rate; WHO = World Health Organization; pts = patients; RD = response duration; G = grade; NA = not available.

[a] Toxicities reported were grade ≥3 hepatic (transaminases only), cutaneous, nausea/vomiting, alopecia, neutropenia, and thrombocytopenia, and all grade 4 toxicities.

[b] Median TTP based on a personal communication from J. Carmichael.

ment (57% of patients pretreated with at least three lines of chemotherapy) and the extensive metastatic disease (visceral disease in 74% of patients, and at least three organ systems involved in 57% of patients) may partly account for this outcome. The fact that patients received a low number of median cycles (2, range 1–8) may also have contributed to the lack of efficacy, even though during infusion, the dose intensity was comparatively adequate (mean dose/infusion = 942 mg/m^2).

While the above-mentioned trials all used a standard infusion time of 30 min, Schmid et al. [20] extended the infusion duration to 6 h and reduced the gemcitabine dose to 250 mg/m^2 and the cycle length to 3 weeks. This trial, performed in variably pretreated patients (0–2+ regi-

mens) produced an overall response rate of 25% (18% of patients with 2+ prior regimens) and a median time to progression of 6.3 months.

As a single agent, gemcitabine is moderately active and well tolerated as first-line and salvage therapy of advanced breast cancer. Toxicity generally consists of mild to moderate myelosuppression with minimal clinical consequences, and minimal nonhematologic toxicity, including hepatic and cutaneous toxicity and alopecia. This tolerability is supported by quality-of-life data that appear essentially unchanged by gemcitabine therapy, with a slight improvement in emotional functioning [14].

On the basis of these findings, gemcitabine adequately fits the expectations of a single agent in the treatment of metastatic breast cancer, and offers a valuable alternative to the palliative treatment of this disease.

Gemcitabine plus Anthracyclines

Anthracycline-based combination chemotherapy has become a standard in the treatment of metastatic breast cancer. Specifically, the FAC regimen, combining 5-fluorouracil, doxorubicin, and cyclophosphamide, may be considered a landmark in terms of efficacy in the first-line setting. In a long-term follow-up of 1,581 patients, this regimen achieved a response rate of 65%, a complete response rate of 17%, and a median progression-free survival of 11.5 months [23].

Doxorubicin's dose-limiting toxicities are myelosuppression, mucositis, and cumulative cardiac toxicity. When gemcitabine is added to doxorubicin, overlapping toxicity is specifically expected with regard to myelosuppression; however, a weekly instead of a monthly application of doxorubicin may reduce toxicity.

First-line chemotherapy with gemcitabine and doxorubicin was studied in a phase II trial conducted by Perez-Manga et al. [24]. Of the 42 patients enrolled, 13 were chemonaive and 29 had received prior adjuvant chemotherapy, which was anthracycline-based in 8 patients. Gemcitabine (800 mg/m^2) and doxorubicin (25 mg/m^2) were both given on days 1, 8 and 15 of a 4-week cycle. In 6 patients, the gemcitabine dose was escalated from 800 to 1,000 mg/m^2. Due to toxicity, only 30 cycles were applied at the higher dose level, and the study was subsequently resumed at the gemcitabine dose of 800 mg/m^2. The overall response rate was 55% (complete response rate of 7%), with 31% of the patients attaining stable disease. The median response duration was 12 months. Apart from notable hematotoxicity, the regimen was well tolerated, as indicated by a low incidence of patient hospitalization, a reduced need for supportive interventions, and the absence of World Health Organization (WHO) grade 3/4 cardiotoxicity. Pharmacokinetic studies indicated that the disposition of both drugs was unchanged when gemcitabine and doxorubicin were administered on the same day. These data clearly indicate that the combination is active, with response rates comparing favorably to those of anthracycline-based combination regimens.

Excellent results were obtained when the gemcitabine/doxorubicin combination was assessed as neoadjuvant therapy. Gomez et al. [25] administered up to three cycles of gemcitabine 1,200 mg/m^2 and doxorubicin 60 mg/m^2, every 3 weeks, followed by surgery or radiotherapy. The overall response rate in 39 chemonaive patients was 95% (complete clinical response rate of 18%). Of the 28 patients who underwent mastectomy because their disease was considered resectable, 3 patients had no evidence of disease upon microscopic evaluation of the mastectomy specimens.

Epirubicin is considered less toxic than doxorubicin, which may allow higher doses in combination regimens. The combination of gemcitabine and epirubicin has been investigated in two phase I trials that have been continued in phase II trials. Using a fixed dose of gemcitabine (1,000 mg/m^2), one study established the recommended dose of epirubicin at 15 mg/m^2, with both drugs given on days 1, 8 and 15 of a 4-week cycle [26]. The other phase I trial evaluated a 3-week schedule of gemcitabine given on days 1 and 8 and epirubicin on day 1 [27]. This schedule appeared to be better tolerated than the 4-week schedule, as the maximum tolerated dose was not reached at gemcitabine 1,500 mg/m^2 and epirubicin 75 mg/m^2. Thus, a phase II trial was initiated that applied a 3-week regimen of gemcitabine 1,500 mg/m^2 and epirubicin 90 mg/m^2 [28]. A preliminary report of these data in 20 patients (first-line therapy in 48% of patients) indicated significant and dose-limiting toxicities that may have contributed to the lower than expected response rate (33%). Therefore, the gemcitabine regimen was changed to 1,250 mg/m^2 on days 1 and 4, while the epirubicin regimen and cycle duration remained the same. Fifteen patients received the modified regimen. Of the 14 evaluable patients, the overall response rate was 60% (updated to 67% at final analysis [unpubl. data]). This regimen was better tolerated than the initial regimen, with fewer dose reductions, grade 4 toxicities, discontinuations due to adverse events, and serious adverse events.

Gemcitabine plus Taxanes

The taxanes docetaxel and paclitaxel promote the formation of tubulin dimers and stabilize microtubules against depolymerization, thereby causing growth inhibition and cell death. The single-agent activities of the taxanes are comparable [5] or superior [2] to that of doxorubicin, the gold standard in breast cancer treatment. In combination therapies, the taxanes have been tested primarily with anthracyclines.

New taxane combinations not based on anthracyclines, however, are sought primarily because patients are increasingly given anthracyclines during adjuvant treatment. Thus, at relapse, patients may have developed anthracycline resistance, as well as cumulative cardiotoxicity with repeated applications of anthracyclines. Furthermore, because paclitaxel prolongs doxorubicin clearance from plasma, its combination with an anthracycline may augment cardiotoxicity.

The rationale for combining gemcitabine with taxanes is not unequivocally supported by preclinical studies. Some results obtained after concurrent or sequential treatment of cell lines with gemcitabine and paclitaxel indicate less than additive or even antagonistic effects [29], while other in vitro results indicate at least additive cytotoxicity [30]. Pharmacologic studies did not reveal any drug interactions at the level of plasma pharmacokinetics [31, 32]; however, paclitaxel appears to increase the accumulation of gemcitabine's active drug metabolite, gemcitabine triphosphate, in mononuclear cells, suggesting that this drug may enhance the cytotoxic effects of gemcitabine in solid tumors [33].

Apart from the apparent inconsistencies of these data, the combination of gemcitabine and paclitaxel is clearly favored on the basis of the different mechanisms of action of the two agents. Moreover, an indication for this drug combination may be appropriate in anthracycline-pretreated patients, in whom high efficacy is still a treatment goal.

Gemcitabine plus Docetaxel

The combination of gemcitabine and docetaxel has been explored using different regimens and under different pretreatment conditions (table 2). Single-agent docetaxel has produced overall response rates of 40–68% [34, 35] in previously untreated patients and 30–42% in patients previously exposed to anthracycline chemotherapy [36]. Although more frequent responses are observed at the higher doses of docetaxel, its use is often limited by toxicity. The dominant dose-limiting toxicity of docetaxel is hematotoxicity (mainly neutropenia), followed by other side effects, such as diarrhea and fluid retention. Thus, depending on dose and schedule, significant hematotoxicity may be encountered when gemcitabine is combined with docetaxel [37, 38].

Two studies assessed gemcitabine plus docetaxel in chemonaive [39] and predominantly chemonaive [38] patients using 2- and 4-week regimens, respectively. Pelegri et al. [39] applied gemcitabine at 2,500 mg/m^2 and docetaxel at 65 mg/m^2, every 14 days. This regimen produced an overall response rate of 72% and grade 3/4 neutropenia in approximately half of the patients. Kornek et al. [38] administered lower doses of gemcitabine (1,500 mg/m^2) and docetaxel (50 mg/m^2) at biweekly intervals; granulocyte colony-stimulating factor (G-CSF) was administered depending on patients' granulocyte nadirs. The overall response rate was 64% for the 25 chemonaive patients and 59% for all 34 evaluable patients. Median time to progression was 7 months. Hematotoxicity was generally manageable, presumably because of the use of G-CSF, although septicemia occurred in 9% of patients.

The combination was also assessed as second- or third-line therapy after relapse or progression with anthracycline and/or taxane chemotherapy [40–43]. These studies treated patients with 3-week regimens of gemcitabine at 900 or 1,000 mg/m^2 and docetaxel from 75 to 100 mg/m^2. Overall response rates varied from 36 to 72%, with the highest response rate achieved at the 100-mg/m^2 docetaxel dose without G-CSF prophylaxis [43]. Median times to progression, reported in three of the four studies, ranged from 6 to 8 months. Interestingly, the combination produced partial responses in 4 patients who progressed during pretreatment with docetaxel or paclitaxel [41], and partial and complete responses in 72% of patients who either attained stable disease or progressed during initial docetaxel treatment [43].

The highest response rate achieved so far (79%) occurred with a 4-week application of gemcitabine 800 mg/m^2 on days 1, 8 and 15 and docetaxel 100 mg/m^2 on day 1 [37]. Most patients were pretreated with anthracyclines in the adjuvant setting. Responses were durable with nearly all responders progression-free for more than 6 months. As growth factor use was avoided in an effort to maintain dose intensity, the hematotoxicity was significant (97% of patients with grade 3/4 neutropenia) but manageable.

These studies demonstrate that the combination of gemcitabine and docetaxel may serve as a potent salvage regimen after anthracycline and/or taxane pretreatment. Durable responses of up to 79% in pretreated patients are achievable. Median times to progression (on the order of 7 months) are consistent across various regimens and

Table 2. Gemcitabine plus docetaxel

Reference (first author)	N/Resp eval	Prior chemotherapy	Study dose mg/m^2	Median TTP months	ORR, %	WHO grade 3 or 4 toxicity[a], n or % of patients
Laufman [37]	39/39	1st-line 7 pts Adjuvant 30 pts Both 2 pts Anthracyclines 33 pts	Gem 800 d1, 8, 15 Doc 100 d1 q 4 wks	NA	79	*G3/4:* neutropenia (39 neutropenic fever in 3), mucositis (2); *G3 only:* thrombocytopenia (1), nausea/vomiting (2)
Kornek [38]	52/34	1st-line 43 pts 2nd-line 9 pts	Gem 1,500 d1, 15 Doc 50 d1, 15 q 4 wks G-CSF	7	59 (median RD = 5 mos) 1st-line: 64 (16/25)	*G3:* neutropenia (4); *G4:* neutropenia (6); *Mild to moderate (grade NA):* alopecia (68%), nausea/vomiting (35%), skin reactions (35%), septicemia (9%)
Pelegri [39]	36/25 (29 toxicity eval)	1st-line 36 pts Adjuvant 14 pts Anthracyclines 10 pts	Gem 2,500 d1 Doc 65 d1 q 2 wks	NA	72	*G3:* neutropenia (7; febrile 1), thrombocytopenia (1), liver (2); *G4:* neutropenia (6)
Brandi [40]	37/30	2nd-line 13 pts ≥ 3rd-line 17 pts (all pts failed on, or relapsed after, first-line anthracycline-based CT)	Gem 1,000 d1, 8 Doc 80 d8 q 3 wks	6	60 (median RD = 5 mos)	*G3/4:* neutropenia (33%), thrombocytopenia (4%), nausea/vomiting (4%); *G2/3:* alopecia (93%)
Mavroudis [41]	52/52	2nd-line 27 pts ≥ 3rd-line 25 pts (all pts failed on, or relapsed after, first-line anthracycline-based CT) Neoadjuvant 6 pts Adjuvant 23 pts Taxanes 25 pts	Gem 900 d1, 8 Doc 100 d8 q 3 wks G-CSF (mandatory)	8	54 (median RD = 3.6 mos) Prior taxanes: 44 (11/25 pts)	*G3:* neutropenia (10; neutropenic fever in 4), thrombocytopenia (9), nausea/vomiting (1); *G4:* neutropenia (5), thrombocytopenia (2)
Fountzilas [42]	40/39	2nd-line 20 pts Adjuvant 3 pts Both 16 pts (all anthracycline-resistant)	Gem 1,000 d1, 8 Doc 75 d1 q 3 wks G-CSF	7	36 (median RD = 10.3 mos) 2nd-line: 35 (7/20) Adjuvant: 33 (1/3) Both: 38 (6/16)	*G3:* neutropenia (7; febrile neutropenia 7), thrombocytopenia (1), nausea/vomiting (3), alopecia (30), dermatitis (1); *G4:* neutropenia (12), thrombocytopenia (1)
Alexopoulos [43]	36/36	2nd- or 3rd-line (anthracycline-containing regimens plus taxanes in 50% of pts)	Gem 900 d1, 8 Doc 100 (schedule NA) q 3 wks	NA	72 (median RD = 3.2 mos)	None reported

Resp eval = Response evaluable; TTP = time to progression; ORR = overall response rate; pts = patients; RD = response duration; G = grade; Gem = gemcitabine; Doc = docetaxel; G-CSF = granulocyte colony-stimulating factor; CT = chemotherapy; NA = not available.

[a] Toxicities reported were grade ≥ 3 hepatic (transaminases only), cutaneous, nausea/vomiting, alopecia, neutropenia, and thrombocytopenia, and all grade 4 toxicities.

conditions of pretreatment. These results are an improvement over those of single-agent docetaxel, and could indicate clinical synergism, particularly because patients responded to gemcitabine/docetaxel even after pretreatment, and in some cases after progressing during docetaxel treatment. The toxicity of the combination is manageable, with hematotoxicity appearing dependent on the dose and schedule of the regimen.

Gemcitabine plus Paclitaxel

Single-agent paclitaxel has produced overall response rates of 32–62% in previously untreated patients [44–46], and 6–48% in anthracycline-resistant patients [47–49]. The addition of gemcitabine to paclitaxel is especially interesting because paclitaxel is less hematotoxic than docetaxel at standard doses for each. Overlapping hematotoxicity between gemcitabine and paclitaxel should therefore be less pronounced. The feasibility of combin-

Table 3. Gemcitabine plus paclitaxel

Reference (first author)	N/Resp eval	Prior chemotherapy	Study dose mg/m^2	Median TTP months	ORR, %	WHO grade 3 or 4 toxicity[a], n or % of patients
Colomer [50]	43/38 (34 toxicity eval)	1st-line 43 pts Adjuvant 24 pts	Gem 2,500 d1 Pac 150 (3 hr) d1 q 2 wks	NA	68	*G3:* neutropenia (5), thrombocytopenia (2), nausea (2), vomiting (2 pts), liver transaminases (2); *G4:* neutropenia (6), lymphocytes (2), leukopenia (3), fever and neutropenia (1)
Delfino [51]	42/42	1st-line 42 pts Adjuvant 27 pts	Gem 1,200 d1, 8 Pac 175 (3 h) d1 q 3 wks	NA	55 (median RD = 19 mos)	Leukopenia and thrombocytopenia (6 each), mucositis (7)
Genot [52]	40/36	1st-line 40 pts	Gem 1,200 d1, 8 Pac 175 (3 h) d1 q 3 wks	7.5	42 (median RD = 11.5 mos)	*G4:* neutropenia (41 events); *G3:* leukopenia (52 events); neutropenia (24 events)
Sanchez [53]	44/44	2nd-line 44 pts Anthracyclines 41 pts Pac 9 pts	Gem 2,500 d1, 15 Pac 135 (3 h) d1, 15 q 4 wks	7	45	*G3/4:* hematologic toxicity (15% of cycles)
Murad [54]	29/29	Second or third relapse during anthracycline-based CT	Gem 1,000 d1, 8 Pac 175 (3 h) d1 q 3 wks (initial regimen was Gem 1,000 on d1, 8, 15 with same Pac dose over 4 weeks. This was changed to 3 weeks with the day-15 dose dropped after unacceptable toxicity (thrombocytopenia) in the first 5 pts)	NA	55 (median RD = 8 mos)	*G3:* neutropenia (6% of cycles), thrombocytopenia (5% of cycles), nausea/vomiting (6% of cycles), alopecia (76% of cycles); *G4:* neutropenia (3% of cycles; 2 pts w/fever), thrombocytopenia (3% of cycles), infection (3% of cycles)

Resp eval = Response evaluable; TTP = time to progression; ORR = overall response rate; WHO = World Health Organization; pts = patients; RD = response duration; G = grade; Gem = gemcitabine; Pac = paclitaxel; NA = not available.

[a] Toxicities reported were grade ≥ 3 hepatic (transaminases only), cutaneous, nausea/vomiting, alopecia, neutropenia, and thrombocytopenia, and all grade 4 toxicities.

ing gemcitabine with paclitaxel has been assessed in chemonaive and pretreated patients (table 3).

Colomer et al. [50] administered a first-line regimen of gemcitabine 2,500 mg/m^2 and paclitaxel 150 mg/m^2 both given on day 1, every 2 weeks. Most patients completed adjuvant chemotherapy ≤ 12 months before relapse. The overall response rate in 38 evaluable patients was 68%. Hematologic toxicity was mainly limited to neutropenia (32% of patients), with only one report of neutropenic fever.

Two additional studies of the combination as first-line therapy for metastatic disease [51, 52] yielded response rates of 55 and 42%, respectively, using identical 3-week regimens of 1,200 mg/m^2 gemcitabine and 175 mg/m^2 paclitaxel. Responses were durable with median response durations of about 1 year or better (19 and 11.5 months, respectively). One study reported a median time to progression of 7.5 months [52].

Sanchez et al. [53] assessed a 4-week schedule of paclitaxel at 135 mg/m^2 and gemcitabine at 2,500 mg/m^2, with both drugs delivered on days 1 and 15. Patients were heavily pretreated for metastatic disease (93% with anthracycline-based regimens). An overall response rate of 45% was reached, but about a third of the patients required growth factors to continue receiving the planned dosing schedule. The median time to progression was 7 months.

Murad et al. [54] conducted a trial in patients who relapsed a second or third time after anthracycline-based chemotherapy. Initially, a 4-week regimen of gemcitabine at 1,000 mg/m^2 and paclitaxel at 175 mg/m^2 was given on day 1 (paclitaxel only), 8 and 15. Severe thrombocytopenia was observed in the first 5 patients, necessitating a change in the treatment schedule from 4 to 3 weeks, with the day-15 gemcitabine dose withdrawn. In these heavily pretreated patients, the overall response rate was 55%

Table 4. Gemcitabine plus vinorelbine

Reference (first author)	N/Resp eval	Prior chemotherapy	Study dose mg/m^2	Median TTP, months	ORR, %	WHO grade 3 or 4 toxicity[a], n or % of patients
Haider [58]	45/45	1st-line 45 pts 2nd-line 15 pts (anthracyclines 10 pts)	Gem 1,000 d1, 15, 21 Vin 40 d1, 21 q 4 wks G-CSF	8.5 1st-line: 9.5 2nd-line: 7	52 (median RD = 8.5 mos) 1st-line 56 (25/45) 2nd-line 40 (6/15)	*G3:* neutropenia (9), nausea/vomiting (3); *G4:* neutropenia (2), leukopenia (1)
Valenza [59]	29/29	2nd-line 29 pts Anthracycline/taxane Adjuvant 25 pts	Gem 1,000 d1, 8, 15 Vin 25 d1, 8 q 4 wks	6.8+ (mean)	48	*G3:* thrombocytopenia (3)
Stathopoulos [60]	51/50	2nd-line 51 pts Anthracycline-based CT Anthracycline/taxane 25 pts	Gem 1,000 d1 15 Vin 25 d1, 15 q 4 wks	6	54 (median RD = 6 mos)	*G3/4:* neutropenia (4)
Nicolaides [61]	31/27	2nd-line 31 pts Taxane-based CT	Gem 1,000 d1, 8 Vin 30 d1, 8 q 3 wks	3.5	22 (median RD = 6 mos)	*G3/4:* neutropenia (15), thrombocytopenia (1), paralytic ileus (1), rash (3)
Mariani [62][b]	31/27	2nd- or ≥ 3rd-line (at least 90% of pts) Anthracycline- and/or taxane-based CT	Gem 1,200 d1, 8 Vin 30 d1, 8 q 3 wks	NA	22	*G3/4:* neutropenia (15), thrombocytopenia (2)
Donadio [63]	26/23	2nd-line 21 pts 3rd-line 5 pts Anthracyclines 12 pts Adjuvant and/or neoadjuvant 19 pts	Gem 1,000 d1, 8 Vin 25 d1, 8 q 3 wks	NA	39	None reported
Moser [64]	69/30 (38 toxicity eval)	1st-line 25 pts 2nd-line 13 pts Anthracycline- and/or taxane-based CT 11 pts	Gem 1,200 d1, 8 Vin 25 d1, 8 q 3 wks	NA	30	*G3/4:* neutropenia (7), phlebitis (1)
Gokmen [65]	26/22	1st-line 6 pts 2nd-line 13 pts 3rd-line 7 pts Anthracycline refractory or resistant 96% of pts	Gem 1,200 d1, 8 Vin 30 d1, 8 q 3 wks	5.5	45	*G3:* thrombocytopenia (4), phlebitis (2); *G4:* leukopenia (1)

Resp eval = Response evaluable; TTP = time to progression; ORR = overall response rate; WHO = World Health Organization; CT = chemotherapy; Gem = gemcitabine; Vin = vinorelbine; G-CSF = granulocyte colony-stimulating factor; RD = response duration; G = grade; pts = patients; NA = not available.

[a] Toxicities reported were grade ≥ 3 hepatic (transaminases only), cutaneous, nausea/vomiting, alopecia, neutropenia, and thrombocytopenia, and all grade 4 toxicities.

[b] For this phase I/II study, only phase II data are presented.

with a median duration of response of 8 months. Grade 3/4 neutropenia was reported in 30% of patients, which was accompanied by neutropenic fever in 14% of patients.

These results demonstrate that the combination of gemcitabine and paclitaxel is effective in both chemonaive and heavily pretreated patients. High and durable responses across different regimens are achievable. Toxicities are manageable, with neutropenia being the main toxicity. The response rate of 55% obtained in anthracycline-pretreated patients [54] may be particularly appreciated in view of the low response rate to single-agent paclitaxel (16%) observed after doxorubicin failure in a phase III study [3]. Although preclinical data do not provide an established basis for synergistic drug interaction, these clinical data clearly support the use of this combination.

Gemcitabine plus Vinorelbine

Vinorelbine exerts antitumor activity through destabilization of microtubules. While this drug has shown good efficacy as first-line treatment (40–60%) [55], activity

after anthracycline pretreatment has only been moderate (16%) [56, 57]. Vinorelbine is characterized by a favorable profile of side effects, with low rates of nausea and emesis, and almost no alopecia. The dose-limiting toxicity of vinorelbine is in the form of noncumulative hematotoxicity. The potential of adding gemcitabine to vinorelbine, two well-tolerated agents with different mechanisms of action, has been explored in various phase II studies (table 4).

Haider et al. [58] conducted the only study that evaluated gemcitabine plus vinorelbine separately as first-line therapy. In a subgroup of 45 chemonaive patients, a 4-week regimen of gemcitabine 1,000 mg/m^2 and vinorelbine 40 mg/m^2 together with G-CSF support produced an overall response rate of 56% and a median time to progression of 9.5 months. In the remaining 15 patients who were pretreated with palliative therapy (including anthracyclines in 10 patients), lower values of response rate (40%) and median time to progression (7 months) were reported.

Two additional studies that applied 4-week regimens of gemcitabine plus vinorelbine, but solely as second-line therapy (after anthracyclines ± taxanes), achieved response rates of 48 and 54%, respectively [59, 60]. Three-week regimens using identical schedules but slightly different doses of gemcitabine or vinorelbine as second- or third-line therapy produced lower response rates of 22% [61, 62] or 39% [63].

Two studies evaluated 3-week regimens in variably pretreated patients (0–2 prior regimens) [64, 65]. Preliminary data reported by Moser et al. [64] in 38 eligible patients (66% chemonaive), indicated an overall remission rate of 30% in 30 evaluable patients. Gokmen et al. [65] used an identical regimen except for a slightly higher dose of vinorelbine (30 vs. 25 mg/m^2). Most patients had undergone one to two prior chemotherapies, although the pretreatment pattern was not uniform with the combination administered as first-line therapy in 23%, as second-line therapy in 50%, and as third-line therapy in 27% of patients. Anthracycline resistance was described in 31% of patients, and anthracycline-refractory disease in 65% of patients. In these predominantly anthracycline-exposed patients, the combination of gemcitabine and vinorelbine achieved a response rate of 45% accompanied by a median time to progression of 5.5 months.

These studies demonstrate that the combination of gemcitabine and vinorelbine is active not only as first-line treatment but also after pretreatment with anthracycline- or anthracycline/taxane-based regimens. Response rates of up to 54% in anthracycline-pretreated patients are achievable. Hematotoxicity, the main toxicity of this combination, appears manageable and generally does not require the use of hematopoietic growth factors.

Gemcitabine plus Vindesine

Vindesine is a known spindle toxin, with a mechanism of action comparable to vinorelbine. While drug application every 3 weeks may be considered an advantage of this agent, neurotoxicity is more pronounced compared to that of vinorelbine. Cazzaniga et al. [66] conducted a multicenter phase II trial evaluating a 3-week regimen of gemcitabine (1,000 mg/m^2 on days 1 and 8) combined with vindesine (3 mg/m^2 on day 1). All but 1 of the 42 enrolled patients had prior first-line therapy (21 had anthracyclines with or without taxanes and three had taxanes only). The overall response rate in 25 evaluable patients was 32% (all partial responses); 24% of patients reached stable disease. Grade 3/4 neutropenia was observed in 44% of the patients.

Gemcitabine plus Cisplatin

Until recently, cisplatin did not play a significant role in breast cancer treatment. In five studies analyzing 119 pretreated patients, a mean response rate of 7% was observed [67–71]. Despite its low activity as a single agent in salvage therapy, cisplatin appears to be a viable partner for combination treatment. In fact, it has been successfully tested together with docetaxel, vinorelbine, anti-HER2/*neu* antibody, and recently with gemcitabine (table 5).

Three lines of argument support this combination. First, breast cancer patients treated with standard regimens in the adjuvant or palliative setting will not have been exposed to gemcitabine or cisplatin in most cases. Consequently, the probability of pretreatment-induced drug resistance to these drugs is low. Second, synergistic cytotoxicity has been observed in vitro when adequate repair of cisplatin-induced DNA damage was prevented by gemcitabine [72]. Third, synergistic interaction between anti-HER2/*neu* antibody and cisplatin has been reported both experimentally and in breast cancer patients [73]. Therefore, the addition of trastuzumab, an anti-HER2/*neu* antibody, to gemcitabine/cisplatin might form an effective triplet combination, and thus may offer another treatment option after anthracycline and taxane pretreatment.

Nagourney et al. [74] first described the in vitro synergism of gemcitabine and cisplatin in patients with breast cancer. Synergistic cytotoxicity was observed in 73% of 225 tumor probes (68% originating from pretreated patients). As first-line therapy, the combination of gemcita-

Table 5. Gemcitabine plus cisplatin

Reference (first author)	N/Resp eval	Prior chemotherapy	Study dose mg/m^2	Median TTP, months	ORR, %	WHO grade 3 or 4 toxicity[a], n or % of patients
Calderillo Ruiz [75]	31/31	1st-line 31 pts	Gem 1,200 d1, 8 Cis 75 d1 q 3 wks	NA	80	*G3/4:* neutropenia (20% of cycles), anemia (3% of cycles), thrombocytopenia (2% of cycles), nausea/vomiting (17% of cycles)
Nagourney [76]	30/30	2nd- to 6th-line Anthracyclines 14 pts Taxanes 20 pts	Gem 1,000 Cis 30 d1, 8, 15 q 4 wks (after 12 pts, regimen changed to Gem 750, Cis 30 d1, 8 q 3 wks)	3.5 2nd- or 3rd-line: 5.5 >4th-line: 3.5	50	*G3:* leukopenia (17% of cycles), neutropenia (11% of cycles), anemia (6% of cycles), thrombocytopenia (33% of cycles); *G4:* leukopenia (2% of cycles), neutropenia (4% of cycles), thrombocytopenia (14% of cycles)
Chaudry [77]	28/28	2nd-line 28 pts Anthracycline- and taxane-based CT	Gem 1,000 d1, 8, 15 Cis 25 d1, 8, 15 q 4 wks	NA	39 median RD = 5.3 mos	*G4:* thrombocytopenia (12% of cycles), neutropenia (9% of cycles), nausea/vomiting (4.5% of cycles)
Burch [78]	21/21	2nd-line 21 pts 3rd-line 17 pts Anthracycline or taxane	Gem 1,000 d1, 8, 15 Cis 25 d1, 8, 15 q 4 wks	7.1	29	*G3:* neutropenia (38%), thrombocytopenia (24%); *G4:* neutropenia (43%), thrombocytopenia (38%)
Doroshow [79]	55/44	M: 24 pts (21 eval) 1st-line, 10 pts; 2nd-line 14 pts H: 31 pts (23 eval) >3rd-line (including doxorubicin or a taxane)	Gem 1,000 d2, 8 Cis 25 d1–4 q 3 wks G-CSF (mandatory for H)	1st-line 8.3 mos 2nd-line 3.7 mos >3rd-line 3.5 mos	34 M 43 H 26	*G3:* neutropenia (9), thrombocytopenia (19), vomiting (8); *G4:* neutropenia (30), thrombocytopenia (19), anemia (5)
Galvez [80]	41/41	2nd-line 41 pts Anthracycline-based CT	Gem 1,200 d1, 8, 15 Cis 50 d1 q 4 wks	5.2	49 median RD = 10.6 mos	*G3/4:* thrombocytopenia (47%), neutropenia (48%), anemia (42%), nausea/vomiting (17%), alopecia (77%), nephrotoxicity (9%), neuropathy (11%)

Resp eval = Response evaluable; TTP = time to progression; ORR = overall response rate; WHO = World Health Organization; CT = chemotherapy; RD = response duration; G = grade; pts = patients; Gem = gemcitabine; Cis = cisplatin; NA = not available; M = moderately pretreated; H = heavily pretreated.

[a] Toxicities reported were grade ≥3 hepatic (transaminases only), cutaneous, nausea/vomiting, alopecia, neutropenia, and thrombocytopenia, and all grade 4 toxicities.

bine (1,200 mg/m^2) and cisplatin (75 mg/m^2) given every 3 weeks with cisplatin given once during the cycle (day 1) has proven to be highly effective, reaching a response rate of 80% in one phase II study [75]. Five additional studies performed in moderate to intensively pretreated patients, which used lower doses of cisplatin given repeatedly [76–79] or once [80] during 3- or 4-week cycles, demonstrated a median overall response rate of 39% (range 29–50%). The toxicity profiles of these regimens were moderate, with thrombocytopenia and neutropenia being the main side effects.

At present, an optimal regimen for the treatment of breast cancer has not been determined in a comparative fashion. To optimize synergy, it was suggested to administer 'repeating doublets' of drugs [81] such as the application used in the Nagourney regimen [76], in which both drugs were given on days 1 and 8. The efficacy as well as the hematotoxicity of this drug application appear favorable. If outpatient use is preferred, the lower weekly cisplatin dose (30 mg/m^2) that can be applied in these regimens offers an additional advantage.

Gemcitabine plus Epirubicin/Paclitaxel (GET) or Doxorubicin/Paclitaxel (GAT)

Anthracyclines and the taxanes belong to the most active groups of agents used in breast cancer treatment. In principle, there is no evidence that the addition of a third agent to a doublet truly adds to efficacy more than it adds to toxicity. A major goal of the combined application of GET or GAT was to improve the complete response rate, since it was claimed that patients achieving a complete response to first-line treatment may be good candidates for long-term survival [23]. To date, the GET and GAT trials have been performed exclusively in the first-line setting.

Two phase II studies evaluating GET have been reported [82, 83]. Both studies used identical 3-week regimens of gemcitabine at 1,000 mg/m^2 on days 1 and 4, epirubicin at 90 mg/m^2 on day 1, and paclitaxel 175 mg/m^2 (3-hour infusion) on day 1. A single-institution study by Conte et al. [82] showed that this regimen was highly active, demonstrating an overall response rate of 92% and a complete response rate of 31% after six courses. Additionally, 25 of the 36 enrolled patients received high-dose chemotherapy, providing a final overall response rate of 97% and a complete response rate of 47%. Median time to progression was 21 months (median follow-up 25 months). On the basis of these very optimistic data, GET was subsequently tested in a multicenter setting of 39 patients [83]. After a median of two courses, the overall response rate was 58%, with a complete response rate of 10%. Final response data, after a median of six courses, are not available. The favorable response rates in these two studies were accompanied by considerable hematotoxicity, with WHO grade 3 and 4 neutropenia reported in 64 and 59% of the patients, respectively.

Sanchez-Rovira et al. [84] observed an overall response rate of 83% (complete response rate of 44%) in a single-institution study of the GAT combination administered to 34 patients over a 4-week schedule (day-2 gemcitabine 2,500 mg/m^2 and paclitaxel 135 mg/m^2, day-1 doxorubicin 30 mg/m^2). The median duration of response and the median time to progression were each 14 months. As with GET, this regimen appears highly active but at the expense of toxicity, with 21% of cycles reduced or delayed primarily due to neutropenia, despite the use of G-CSF in 66% of patients.

As a follow-up to this study, Sanchez-Rovira et al. [85, 86] are also conducting a phase II study of the GAT regimen as neoadjuvant therapy in patients with stage II/III invasive breast cancer. Patients received six cycles of GAT prior to surgery and three additional cycles after surgery. An overall response rate of 98% (complete response rate of 42%) has been achieved in 33 assessable patients. The median duration of response was 13+ months.

Gemcitabine plus 5-Fluorouracil/Leucovorin

The combination of the two antimetabolites, gemcitabine and 5-fluorouracil, has shown synergistic cytotoxicity in colorectal tumor cell lines in vitro [87]. Meanwhile, much knowledge regarding this combination in pancreatic cancer has been accumulated. While toxicity has been generally moderate, it is unclear whether this drug combination is superior to that of single-agent gemcitabine.

The approach of combining gemcitabine and 5-fluorouracil in breast cancer is primarily based on the good tolerability and efficacy of both drugs in this tumor entity. Thus far, one study of the gemcitabine/5-fluorouracil/leucovorin combination has been conducted. Mulkerin et al. [88] administered gemcitabine 1,000 mg/m^2, 5-fluorouracil 600 mg/m^2, and leucovorin 20 mg/m^2 over 4-week cycles with all drugs given on days 1, 8 and 15. Most patients were pretreated with adjuvant and/or metastatic chemotherapy. This regimen was only moderately active, producing an overall response rate of 22% in 27 evaluable patients. Leukopenia was the predominant toxicity. Considering that gemcitabine treatment alone achieved response rates of up to 42% in pretreated patients (table 1), there is presently no indication that the addition of 5-fluorouracil improves efficacy.

Gemcitabine plus 5-Fluorouracil/Leucovorin and Cyclophosphamide

In the phase I portion of a phase I/II study, gemcitabine (1,000 mg/m^2) was combined with 5-fluorouracil (425 mg/m^2), folinic acid (100 mg/m^2), and escalating doses of cyclophosphamide [89]. All drugs were applied on days 1 and 8 of a 3-week cycle. The subsequent phase II portion used a cyclophosphamide dose of 800 mg/m^2 supported by G-CSF. In 21 evaluable patients refractory to anthracycline- and taxane-based chemotherapy, an overall response rate of 43% and a WHO grade 3/4 neutropenia rate of 34% were reported.

Gemcitabine plus a Biologic Agent: Trastuzumab

Gemcitabine has also been combined with paclitaxel plus the biologic agent trastuzumab as first-line therapy for patients with newly diagnosed HER2/*neu*-overexpressing metastatic breast cancer. In preclinical studies, trastuzumab was found to have additive [90] to synergistic [91] effects with some chemotherapeutic agents in tumor cell lines. Clinical trials in HER2-positive breast cancer patients have demonstrated that trastuzumab combined with cytotoxic chemotherapy is associated with improved time to disease progression and overall survival [92].

In a first-line study conducted by the Hossier Oncology Group (HOG) [93], 27 patients (target enrollment of 46) received a triplet regimen consisting of paclitaxel 175 mg/m^2 over 3 h on day 1, gemcitabine 1,200 mg/m^2 on days 1 and 8, and trastuzumab at a 4-mg/kg loading dose on day 1 followed by 2 mg/kg/week, every 21 days. A partial response was achieved in 92% of 13 evaluable patients, and only 1 patient has progressed. The treatment has been

Table 6. Phase III studies planned or in progress: Gemcitabine/taxane combinations in metastatic breast cancer

Location or cooperative group	Population	Approximate number	Regimens (doses in mg/m^2, all 21-day cycles)
Global	First-line Prior adjuvant (anthracycline)	500	Gem 1,250 d1 plus Pac 175 d1 vs. Pac 175 d1
Danish Breast Cancer Cooperative Group	First- or second-line (prior anthracycline)	300	Gem 1,000 d1, 8 plus Doc 75 d8 vs. Doc 100 d1
Finnish Cooperative Group	First-line	240	Gem 1,000 d1, 8 alternating with Doc 100 d1 vs. Doc 100 d1
United States[a]	First- or second-line (prior anthracycline)	440	Gem 1,000 d1, 8 plus Doc 75 d1 vs. Doc 75 d1 plus Cap 2,000 or 2,500 d1–14
United States	Second-line (prior anthracycline)	210	Gem 1,000 d1, 8 plus Doc 75 d1 vs. Gem 1,000 d1, 8 plus Vin 25 d1, 8
Asia/Pacific	First- or second-line (prior anthracycline)	210	Gem 1,250 d1, 8 plus Pac 175 d1 vs. Gem 1,000 d1, 8 plus Pac 100 d1, 8 vs. Gem 1,000 d1, 8 plus Doc 40 d1, 8

Gem = Gemcitabine; Pac = paclitaxel; Doc = docetaxel; Cap = capecitabine; Vin = vinorelbine.

[a] A similar study is also being conducted in the European Union.

well tolerated, with grade 4 toxicity limited to myelosuppression.

O'Shaughnessy et al. [94] are conducting a phase II study of gemcitabine 1,200 mg/m^2 (days 1 and 8) combined with trastuzumab as a 4-mg/kg loading dose, followed by 2 mg/kg/week thereafter, in 55 heavily pretreated patients with HER2-positive metastatic breast cancer. Cycles were administered every 21 days. Among the 38 assessable patients, 12 had partial responses, for an overall response rate of 32; 40 (6/15) and 26% (6/23) of responders were HER2 ++ and +++, respectively. Median time to progression was 6.7 months. The primary grade 3/4 toxicity was neutropenia, which occurred in 9 patients.

Future Directions

Due to increasing anthracycline resistance and the risk of cumulative cardiotoxicity associated with anthracyclines, the development of non-anthracycline-containing regimens in the treatment of metastatic breast cancer is clearly needed. As a single agent, gemcitabine (1) is active and well tolerated even as salvage therapy, (2) can be easily combined with other agents without the confounding effects of cross-resistance and overlapping toxicity, and (3) has shown synergistic potential with various cytotoxic as well as biologic agents. Thus, phase III trials are planned or under way to confirm the increased efficacy and manageable toxicity of gemcitabine when added to non-anthracycline agents with proven single-agent activity.

On the basis of phase II study results, combinations of gemcitabine with taxanes appear to offer the most favorable balance between efficacy and tolerability. These regimens, particularly the two-drug combinations, have demonstrated durable, high response rates and consistent median times to disease progression under various pretreatment conditions, without significantly compromising tolerability. Various phase III studies are planned or in progress to establish the role of gemcitabine in combination with a taxane as first-line or salvage therapy (table 6).

In a large randomized trial by the Central European Cooperative Oncology Group comparing the GET regimen to the triplet combination of 5-fluorouracil/epirubicin/cyclophosphamide (FEC) [95], the clinical value of the triple-agent approach is being tested as first-line chemotherapy. An interim analysis of toxicity performed on 22 patients has demonstrated that the administration of the GET regimen is unproblematic in the multicenter setting; the need for G-CSF support is rare. Neutropenia grade 3/4 was comparable in the GET and FEC arms (63 vs. 69%, respectively).

Thus far, GET and GAT trials have been performed exclusively in the first-line setting, and have yielded high response rates, perhaps at the expense of acceptable hematotoxicity. The potential of these dose-dense combinations as conditioning regimens for high-dose chemotherapy and/or stem cell support should be affirmed in phase III trials.

Summary and Conclusion

The rationale for gemcitabine-based combination treatment is supported by its unique mechanism of action, which makes drug resistance to standard pretreatment improbable, and its potential for synergistic drug interactions. Numerous trials have demonstrated activity of gemcitabine in the treatment of breast cancer. Gemcitabine has proven activity as a well-tolerated single agent and even as salvage therapy in intensively pretreated patients. It may be useful in patients who choose palliation without many side effects, particularly as its use is not precluded by cumulative organ toxicity. Its combination with cytotoxic agents such as doxorubicin, the taxanes, vinorelbine, vindesine, or cisplatin, and targeted therapy such as trastuzumab, provides feasible options with added activity.

Specifically, gemcitabine combinations provide new options in anthracycline- and taxane-pretreated patients. Gemcitabine plus taxane regimens appear to offer the most favorable balance between efficacy and tolerability. Various confirmatory phase III trials including gemcitabine/taxane combinations are planned or in progress. In addition, single-agent gemcitabine is being studied as alternating therapy with taxanes in the first-line setting and also with targeted agents.

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