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Gemcitabine plus taxane combinations in metastatic breast cancer: a comprehensive review

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Abstract

Gemcitabine and the taxanes (paclitaxel and docetaxel) exhibit a synergistic anticancer activity and are active in the treatment of metastatic breast cancer. Many trials have investigated the efficacy and toxicity of gemcitabine plus paclitaxel, including one Phase III trial. Gemcitabine has also been studied in combination with docetaxel and again, in a Phase III trial. In first-line Phase II trials, 61% of patients responded to gemcitabine plus paclitaxel therapy and 64% have responded to gemcitabine plus docetaxel. Response rates were lower among patients who had received previous chemotherapy for metastatic disease (46% and 52%, respectively). Toxicity of the gemcitabine plus paclitaxel regimens was generally low, with few cases of neutropenia or non-haematological toxicity. Gemcitabine plus docetaxel was seen to be slightly more toxic in terms of neutropenia and fatigue. Results of a randomised Phase III registration trial of gemcitabine plus paclitaxel versus single-agent paclitaxel show a clear advantage for the combination in terms of survival, with little added toxicity. Gemcitabine plus paclitaxel improved overall survival by approximately 25% compared with paclitaxel alone. A Phase III trial comparing gemcitabine plus docetaxel with capecitabine plus docetaxel showed similar efficacy results, with more toxicity in the capecitabine arm. The efficacy of triplet combinations of gemcitabine plus paclitaxel plus an anthracycline or trastuzumab are being explored in the metastatic and neoadjuvant setting with excellent response results. Two very large trials in Europe and the US are evaluating the incorporation of gemcitabine into sequential adjuvant therapy in post-operative breast cancer.

Keywords: Combination chemotherapy; Taxanes; Docetaxel; Paclitaxel; Anthracyclines; Trastuzumab; Gemcitabine; Breast cancer

1. Introduction

Patients with metastatic breast cancer who receive combination chemotherapy have improved relapse-free and overall survival (OS) rates compared with those treated with single-agent chemotherapies [1,2]. Indeed, some patients have long-term remission following treatment with combinations [3]. A substantial percentage of node-negative and node-positive patients with operable breast cancer receive adjuvant anthracycline-containing chemotherapy [4]. Biological and clinical data show that patients with metastatic disease, previously treated with anthracyclines, have a lower chance of therapeutic benefit from further treatment with anthracycline-containing regimens [5,6]. As a result, alternative chemotherapies are used for advanced breast cancer. The taxanes, either as single agents or combined with other drugs, have become the standard front-line therapy for patients with disease progression after anthracycline chemotherapy [7].

The antitumour effect of paclitaxel and docetaxel is chiefly due to their ability to stabilise microtubules and block eukaryotic cells in the G_2/M mitotic phase [7–9]. The taxanes have been shown to be among the most active therapies for advanced breast cancer and are used as adjuvant therapy in node-positive breast cancer [7,10].

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Gemcitabine is a cytosine arabinoside prodrug analogue with anticancer activity in a wide range of tumour types. The cytotoxicity of this agent is related to the cellular accumulation of gemcitabine triphosphate (dFdCTP), which induces G_0/G_1 and S phase arrest in human solid tumour cells. In patients with advanced breast cancer, single-agent gemcitabine has induced response rates of 15–46% with minimal toxicity, even in heavily pre-treated cases [11,12].

The combination of gemcitabine with paclitaxel or docetaxel is particularly successful because gemcitabine and the taxanes have different mechanisms of action and non-overlapping toxicities. *In vivo*, paclitaxel enhances the gemcitabine-related accumulation of dFdCTP [13]. In cancer cell lines, paclitaxel, administered immediately before gemcitabine, significantly increases dFdCTP accumulation, gemcitabine incorporation into RNA and the apoptotic index [14]. Gemcitabine has no effect on paclitaxel plasma pharmacokinetics [15]. The administration sequence of gemcitabine and docetaxel had no significant effect on the toxicity or pharmacokinetics of either drug [16]. Gemcitabine has been shown to have a synergistic relationship with paclitaxel and docetaxel *in vitro* and *in vivo* [17–19].

2. Phase II trials of gemcitabine plus paclitaxel

In Phase I studies of three-weekly gemcitabine plus paclitaxel, febrile neutropenia was shown to be dose limiting in all but one study where alanine transaminase elevations restricted further increases in dose [20]. Phase I studies using bi-weekly schedules found doses of paclitaxel at 150 mg/m^2 and gemcitabine at 3,000 mg/m^2 or 2,500 mg/m^2 to be most successful [21,22].

Phase II trials have explored the toxicity and efficacy of gemcitabine plus paclitaxel. Doses, schedules, response rates and toxicities are summarised in Table 1 [23–29]. Trials were performed in patients receiving first-, second- or third-line therapy for metastatic breast cancer. Administration schedules were every 2 or 3 weeks. Overall response rates (ORR) ranged from 40 to 71%, with the highest rates observed in studies of chemotherapy-na ve patients (61%) compared with patients undergoing second-line therapy (46%).

The combination was generally well tolerated, particularly in the first-line setting. Murad *et al.* observed grade 3/4 neutropenia in 35% of patients, grade 4 neutropenic fever and grade 3 neuropathy in 7% of patients [23]. In a study assessing second- or third-line therapy with gemcitabine plus paclitaxel, 15% of patients experienced grade 3/4 haematological toxicity, and 34% required granulocyte-colony stimulating factor support [24]. Colomer *et al.* observed grade 4 neutropenia in 17% of patients; non-haematological toxicities occurred in <5% of cases, except for elevated liver enzyme levels, which affected 8% of cases [27]. In a study by Delfino *et al.*, grade 3/4 neutropenia and thrombocytopenia were reported in 13% of patients, along with infrequent non-haematological toxicities [28]. Preliminary reports of Phase II gemcitabine plus paclitaxel studies presented at ASCO in 2002 and 2005 showed manageable toxicities [25,26,29]. One study of gemcitabine plus paclitaxel in patients pretreated with docetaxel is of particular interest because three of the 13 observed responses occurred in docetaxel-refractory patients [26].

Colomer *et al.* observed that patients with elevated levels of circulating HER2 extracellular domain had a poorer response to therapy (83% vs 42%; $P = 0.02$), which was the basis for a subsequent Phase II clinical trial of gemcitabine plus paclitaxel plus trastuzumab in this patient group [27].

3. Phase II trials of gemcitabine plus docetaxel

Phase I studies of bi-weekly gemcitabine plus docetaxel found that febrile neutropenia and asthenia were dose limiting. These studies recommended that docetaxel be administered at a dose of 65–75 mg/m^2 in combination with gemcitabine at a dose of 2,000–3,000 mg/m^2 [30–32].

Phase II trials have used high doses of gemcitabine plus docetaxel in patients with metastatic breast cancer (Table 2) [19,33–42]. The scheduling in these trials was varied; some

Table 1
Phase II clinical trials of gemcitabine plus paclitaxel doublets in metastatic breast cancer

Author [ref]	*N*	Gemcitabine dose (mg/m^2)	Paclitaxel dose (mg/m^2)	Schedule	Response rate (%)	Grade 3/4 toxicity (%)			
						Fatigue	Neutropenia	FN	Thrombocytpopenia
Second-line									
Murad [23]	29	800 d1,8,15	175 d1	q3wk	55	0	35	7	8
Sanchez-Rovira [24]	52	2,500 d1	135 d1	q2wk[a]	40	NR	15	2	1
Vici [25]	20	1,500 d1	150 d1	q2wk[a]	45	NR	11	NR	0
Alexopoulos [26]	28	1,500 d1	130 d1	q2wk[a]	47	NR	7	NR	0
First-line									
Colomer [27]	42	2,500 d1	150 d1	q2wk	71	0	29	2	4
Delfino [28]	45	1,200 d1,8	175 d1	q3wk	67	0	13	0	13
Genot [29]	36	1,200 d1,8	175 d1	q3wk	42	NR	34	NR	NR

[a] With granulocyte-colony stimulating factor (G-CSF).
FN: febrile neutropenia; NR: not reported.

Table 2
Phase II clinical trials of gemcitabine plus docetaxel doublets in metastatic breast cancer

Author [ref]	N	Gemcitabine dose (mg/m^2)	Docetaxel dose (mg/m^2)	Schedule	Response rate (%)	Grade 3/4 toxicity (%)			
						Fatigue	Neutropenia	FN	Thrombocytopenia
Second-line									
Mavroudis [33]	52	900 d1,8	100 d8	q3wk	54	2	29	8	21
Fountzilas [34]	39	1,000 d1,8	75 d1	q3wk[a]	36	10	49	18	5
Laufmann [35]	9	800 d1,8,15	100 d1	q4wk	88	–	–	–	–
Lenz [36]	35	1,000 d1,8	75 d1	q3wk	54	2	53	NR	14
Kornek [37]	14	1,500 d1	50 d1	q2wk[a]	43	–	–	–	–
Brandi [38]	53	1,000 d1,8	80 d8	q3wk	53	NR	43	9	6
Slee [39]	38	1,000 d1,8	75 d1	q3wk	60	NR	12	1	1
Alexopoulos [19]	50	900 d1,8	100 d8	q3wk	46	6	38	8	14
First-line									
Pelegr [40]	32	2,500 d1	65 d1	q2wk	66	17	46	6	0
Palmeri [41]	58	800 d1,8,15	35 d1,8,15	q4wk	64	2	14	0	7
Laufmann [35]	30	800 d1,8,15	100 d1	q4wk	79	33	92	8	3
Kornek [37]	38	1,500 d1	50 d1	q2wk[a]	60	0	29	4	0
Mavroudis [42]	52	1,500 d1	65 d1	q2wk	59	8	43	4	6

[a] With granulocyte-colony stimulating factor (G-CSF).
FN: febrile neutropenia.

trials administered gemcitabine on days 1 and 8, with docetaxel given on day 1 or 8. In one trial, chemotherapy was given weekly for 3 weeks, followed by a week of rest [41]. Three studies used a bi-weekly administration [37,40, 42]. The ORR ranged from 36% to 79%; higher mean ORRs were observed in first-line therapy trials (64%) compared with second-line trials (52%). Alexopoulos *et al.* evaluated the ORR of gemcitabine plus docetaxel in 50 docetaxel-resistant or refractory patients. Of these, 30 patients were previously stable and 20 had progressive disease [19]. A response was observed in 46% of patients (40% in the refractory cases), indicating that the combination has an *in vivo* synergistic effect.

Gemcitabine plus docetaxel was well tolerated, although toxicity was slightly more pronounced in the second-line setting; grade 3/4 neutropenia was generally observed in approximately 30–50% of cases, febrile neutropenia occurred in about 10% of cycles and thrombocytopenia was observed in around 5–10% of cases.

4. Phase III trial of gemcitabine plus paclitaxel

Early results of a randomised trial comparing gemcitabine plus paclitaxel with single-agent paclitaxel have been published [43]. The registration study compared gemcitabine plus paclitaxel with single-agent paclitaxel in 529 metastatic breast cancer patients previously treated with an anthracycline after no previous chemotherapy for advanced disease. The primary study endpoints were OS and time to progression. Secondary objectives were progression-free survival (PFS), ORR, toxicity, quality of life (QoL) and pain palliation. The design of the study is shown in Fig. 1.

The interim analysis shows a statistically significant advantage in terms of OS after treatment with gemcitabine plus paclitaxel compared with paclitaxel alone (18.5 months vs 15.8 months; $P = 0.018$) [43]. The improvement in survival time in the gemcitabine plus paclitaxel arm was approximately 25% (hazard ratio 0.77) (Fig. 2). All other efficacy variables analysed also favoured the gemcitabine plus paclitaxel arm (Table 3). Grade 3/4 haematological toxicities were more pronounced with gemcitabine plus paclitaxel than with paclitaxel alone (Table 4). Non-haematological toxicity was manageable in both arms, with similar toxicity values for neuropathy and slightly higher values for fatigue (6% vs 1%). There was one toxic death per arm.

The survival advantage observed in this study has established a role for gemcitabine in the treatment of metastatic breast cancer and has resulted in the approval of gemcitabine, in combination with paclitaxel, for the treatment of first-line metastatic breast cancer by the European Medicines Agency (EMEA) and the United States Food and Drug Administration (FDA).

5. Phase III trial of gemcitabine plus docetaxel

Results of a European randomised clinical trial comparing gemcitabine plus docetaxel with capecitabine plus docetaxel in anthracycline-pretreated patients with metastatic breast cancer were presented at the ASCO meeting in 2005 [44]. The primary endpoint of the study was PFS; secondary endpoints were ORR, time to treatment failure (TTF), OS, toxicity and QoL. Docetaxel (75 mg/m^2) was administered every 3 weeks, along with either gemcitabine (1,000 mg/m^2) on days 1 and 8 every 3 weeks, or capecitabine (2,500 mg/m^2) on days 1–14. Three-hundred and five patients were randomised and analysed on an intention-to-treat basis (gemcitabine plus docetaxel arm: 153 patients; capecitabine plus docetaxel arm: 152).

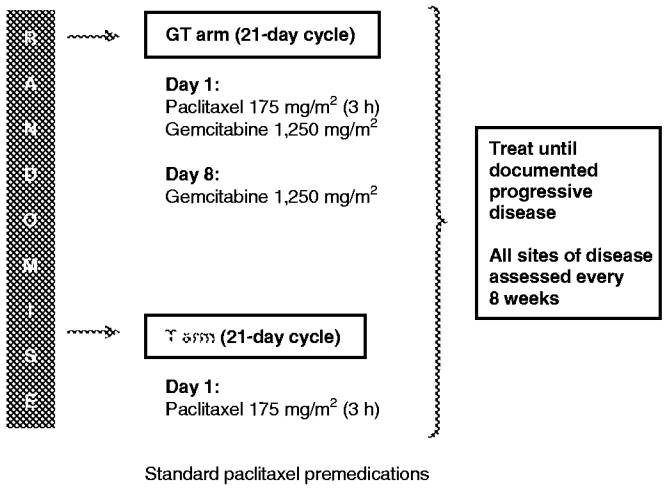

Fig. 1. Study design of Phase III trial comparing gemcitabine plus paclitaxel (GT) versus paclitaxel (T) alone in metastatic breast cancer patients. Study JHQG. Reproduced from Albain *et al.* [43].

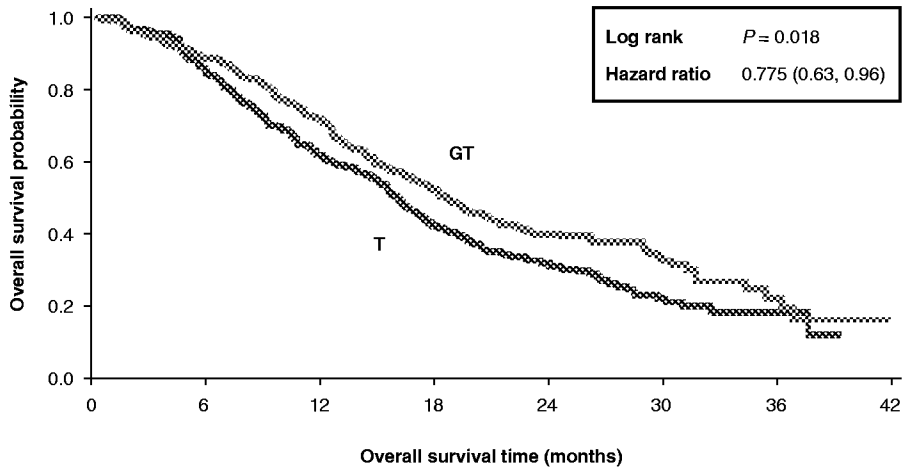

Fig. 2. Overall survival in Phase III trial of gemcitabine plus paclitaxel (GT) versus paclitaxel (T) alone in metastatic breast cancer patients. Study B9E-MC-JHQG. Reproduced from Albain *et al.* [43].

Table 3
Efficacy analysis in Study JHQG comparing gemcitabine plus paclitaxel with paclitaxel alone [42]

	Gemcitabine plus paclitaxel (N = 267)	Paclitaxel alone (N = 262)	P value
Overall response rate (95% CI)	40.8% (34.9–46.7)	22.1% (17.2–27.2)	<0.0001
Time to progression [a] (95% CI)	5.2 months (4.2–8.6)	2.9 months (2.6, 3.7)	<0.0001
Overall survival [a] (95% CI)	18.5 months (16.5, 21.2)	15.8 months (14.4, 17.4)	0.018

CI: confidence interval.
[a] Median values.

Median PFS was equivalent in both arms: 35 weeks in the gemcitabine plus docetaxel arm (95% CI, 29–37 weeks) and 35 weeks in the capecitabine plus docetaxel arm (95% CI, 31–38 weeks). The response rate was 32% in both arms of the study, and median TTF was 19 weeks and 18 weeks,

Table 4
Grade 3/4 haematological toxicities by common toxicity criteria on comparing gemcitabine plus paclitaxel with paclitaxel alone [43]

Grade 3/4 haematological toxicity	Gemcitabine plus paclitaxel	Paclitaxel
Febrile neutropenia	5%	1%
Neutropenia	48%	11%
Thrombocytopenia	5%	0%

respectively. Discontinuation due to drug-related events occurred in 13% of patients treated with gemcitabine plus docetaxel versus 28% of those treated with capecitabine plus docetaxel (P = 0.0014). Grade 3/4 toxicity results are shown in Table 5. The authors concluded that gemcitabine plus docetaxel was similar to capecitabine plus docetaxel in terms of efficacy. However, non-haematological toxicity was found to be lower in the gemcitabine plus docetaxel arm.

Table 5
Grade 3/4 haematological toxicities by common toxicity criteria on comparing gemcitabine plus docetaxel with capecitabine plus docetaxel [44]

Grade 3/4 haematological toxicity	Gemcitabine plus docetaxel	Capecitabine plus docetaxel
Febrile neutropenia	8%	13%
Neutropenia	85%	82%
Thrombocytopenia	10%	3%
Grade 3/4 non-haematological toxicity		
Hand-and-foot syndrome	0%	26%
Diarrhoea	8%	18%
Mucositis	4%	17%

6. Triplet combinations of gemcitabine plus paclitaxel plus an anthracycline or trastuzumab

The addition of an anthracycline to gemcitabine plus paclitaxel in patients with metastatic breast cancer has been explored in Phase II trials (Table 6). Excellent objective response rates have been achieved in single-centre studies with gemcitabine plus doxorubicin plus paclitaxel (GAT) and gemcitabine plus epirubicin plus paclitaxel (GET) (83% and 92%, respectively) and in a multicentre study with GET (71%) [45–47]. Slightly higher toxicity was associated with GAT and GET compared with gemcitabine plus paclitaxel. The results of a randomised comparison of GET versus 5-fluorouracil plus epirubicin plus cyclophosphamide did not show a therapeutic survival advantage for GET in advanced breast cancer [48].

Preliminary results of trials combining gemcitabine with the well-established paclitaxel plus trastuzumab regimen in HER2-positive metastatic breast cancer have been reported by two research groups. Sledge *et al.* reported a 67% response rate using a day 1 and 8 schedule, and Colomer *et al.* presented a 78% response rate using a bi-weekly administration of gemcitabine, paclitaxel and trastuzumab, administered to a group of HER2 extracellular domain positive patients [49,50].

In neoadjuvant trials of taxane plus gemcitabine-containing doublets or triplets, response rates in primary breast cancer patients ranged from 80% to 90% with complete responses in approximately 20%. Trials using GAT and GET reported pathologically complete response rates (pCR) of 17% and 15%, respectively [51,52].

7. Neoadjuvant and adjuvant uses of gemcitabine/taxane combinations

Neoadjuvant and adjuvant use of gemcitabine/taxane combinations are shown in Table 7. Llombart-Cussac *et al.*

Table 6
Phase II clinical trials of gemcitabine plus paclitaxel triplets in metastatic breast cancer

	N	Gemcitabine (mg/m^2)	Paclitaxel (mg/m^2)	3rd drug (mg/m^2)	Schedule	ORR
Gemcitabine plus paclitaxel plus anthracyclines						
Sanchez-Rovira [45]	41	2,500 d1	135 d1	Doxorubicin (30 d1)	q2wk	34 (83%)
Conte [46]	36	1,000 d1,4	175 d1	Epirubicin (90 d1)	q3wk	33 (92%)
Cappuzzo [47]	48	1,000 d1,4	175 d1	Epirubicin (90 d1)	q3wk	34 (71%)
Zielinsky [48] [a]	114	1,000 d1,4	175 d1	Epirubicin (90 d1)	q3wk	71 (62%)
Gemcitabine plus paclitaxel plus trastuzumab						
Sledge [49]	46	1,200 d1,8	175 d1	Trastuzumab (4 mg/kg, then 2 mg/kg/wk)	q3wk	29 (63%)
Colomer [50]	27	2,500 d1	150 d1	Trastuzumab (4 mg/kg, then 2 mg/kg/wk)	q2wk	21 (78%)

[a] Phase III trial comparing GET with FEC; the figures shown belong to the GET arm.
ORR: overall response rate.

Table 7
Phase II combinations of gemcitabine plus taxanes in primary breast cancer

	N	Gemcitabine (mg/m^2)	Taxane (mg/m^2)	3rd drug (mg/m^2)	Schedule	ORR	pCR rate [a] (%)
Gemcitabine plus paclitaxel							
Sanchez-Rovira [51]	46	2,000 d1	135 d1	Doxorubicin (40 d1)	q2wk	43 (93%)	8 (17)
Conte [52]	41	1,000 d1,4	175 d1	Epirubicin (90 d1)	q3wk	36 (88%)	14 (20)
Llombart-Cussac [53]	68	1,500 d1	150 d1	None	q2wk	57 (83%)	14 (20)
Gemcitabine plus docetaxel							
Yardley [54]	34	800 d1,8	30 d1,8	Epirubicin (75 d1)	q3wk	29 (85%)	8 (24)
Schneeweiss [55]	77	800 d1, 8	75 d1	Epirubicin (90 d1)	q3wk	71 (92%)	20 (26)
Schmid [56]	40	350 d4 (4 h CI)	75 d1	NPLDoxo (60 d1)	q3wk	32 (80%)	7 (17.5)
Est vez [57]	24	2,500 d1	65 d1	None	q2wk	19 (79%)	1 (4)

[a] In the breast: includes microscopic foci (<1 mm).
NPLDoxo: non-pegylated liposomal doxorubicin; ORR: overall response rate; pCR: pathologically complete response.

described a Phase II pharmacogenomic study using a bi-weekly gemcitabine plus paclitaxel schedule, and reported a pCR of 14% where the taxane paclitaxel was employed [53].

Higher pCRs have been reported for gemcitabine plus docetaxel combinations. Yardley *et al.*, for example, recorded a value of 24% with gemcitabine plus docetaxel in metastatic and neoadjuvant treatment, whereas Schneeweiss *et al.* reported a pCR of 26% for gemcitabine, epirubicin and docetaxel as primary systemic therapy. However, other trials have reported lower response rates [54–57].

The 'tAnGo' Phase III study is exploring the use of gemcitabine plus paclitaxel in sequential adjuvant chemotherapy in post-operative patients. The study uses a regimen of epirubicin plus cyclophosphamide followed by gemcitabine plus paclitaxel or single-agent paclitaxel [58]. A total of 3,152 patients have been recruited into this trial and entry was closed in December 2004. The toxicity data from this study show that the tAnGo regimens were well tolerated. The preliminary safety evaluation in the first 130 cases showed that adding gemcitabine to paclitaxel did not induce new or unexpected toxicities in the lung, heart, liver or skin. There were no amendments to the study protocol due to safety concerns. Analysis of the efficacy data from this study, based on disease-free survival, is currently under way and the results and conclusions of the trial should be available soon.

A second Phase III study (NSABP B-38) is also under way and compares three adjuvant chemotherapy regimens in women with early breast cancer [59]. Patients were randomly assigned to three treatment arms. Patients in the first group received doxorubicin plus cyclophosphamide/docetaxel on day 1 every 21 days for six cycles. Group two received doxorubicin plus cyclophosphamide on day 1 every 14 days for four cycles, followed, 14 days later, by paclitaxel. Group three received doxorubicin plus cyclophosphamide on day 1 every 14 days for four cycles, followed, 14 days later, with gemcitabine plus paclitaxel every 14 days for four cycles. All patients with oestradiol receptor-positive and/or progesterone receptor-positive tumours received hormonal therapy comprising tamoxifen and/or an aromatase inhibitor 3–12 weeks after the last dose of chemotherapy. No results from this trial are currently available. Present accrual is approximately 800 with a target accrual of 3,400 patients.

8. Conclusion

Gemcitabine, in combination with paclitaxel or docetaxel, represents a new therapeutic option for patients with metastatic breast cancer. In advanced breast cancer, gemcitabine plus paclitaxel has demonstrated an increase in overall patient survival of approximately 23%, compared with paclitaxel alone. This outcome has prompted EMEA and FDA to approve gemcitabine plus paclitaxel for the first-line treatment of patients with metastatic breast cancer after failure of prior anthracycline-containing adjuvant chemotherapy. The combination of gemcitabine plus docetaxel offers another treatment possibility with similar efficacy to the gemcitabine plus paclitaxel combination, albeit with slightly more toxicity. The addition of an anthracycline to gemcitabine paclitaxel plus docetaxel combinations increases response rates further; these triplet combinations have shown great promise in the neoadjuvant setting. In HER2 positive patients, trastuzumab, when added to gemcitabine plus taxane combinations, also achieves promising results. Finally, adjuvant clinical trials will soon determine the role of gemcitabine plus taxane combinations in the post-operative treatment of early breast cancer.

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