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# Clinical considerations in the optimisation of gemcitabine plus taxane as first-line treatment for metastatic breast cancer

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ABSTRACT

Combining gemcitabine with a taxane has produced impressive results in metastatic breast cancer: gemcitabine plus paclitaxel has shown good efficacy with respect to response rates, time to disease progression and overall survival; gemcitabine plus docetaxel also offers an effective option. Both gemcitabine combinations are less toxic than capecitabine plus docetaxel, and efficacy is unlikely to be compromised by selecting one gemcitabine plus taxane combination over the other. In the majority of trials, taxane combinations have led to significantly better overall survival than taxane monotherapy. One option for optimising gemcitabine plus taxane combinations is to increase dose density: a dose-dense schedule can achieve a greater and often more rapid reduction in tumour burden, without the risk of regrowth. Trials are also under way to compare bi-weekly schedules with standard schedules. One further option is to combine gemcitabine plus taxane with molecular-targeting agents, which has shown promising preliminary data, and trial results are eagerly awaited.



## 1. Introduction

Breast cancer is the leading cause of cancer death in women, and one of the most commonly diagnosed types of cancer[1]. This article outlines the current clinical considerations for optimising combinations of gemcitabine plus a taxane for the first-line treatment of metastatic breast cancer (MBC).

In 2006, recommendations were made for treating MBC patients based on agreed conclusions from the *Second Consensus Development Conference on the Treatment of Metastatic Breast Cancer*[2] organised by the Central European Cooperative Oncology Group (CECOG). The guidelines recommend that patients who have not previously received anthracycline-based chemotherapy should receive it. Further, it is proposed that in patients who have relapsed more than 12 months after receiving anthracycline pre-treatment, a re-introduction of therapy should be attempted while ensuring that the cumulative dose is carefully monitored. It is also suggested that anthracycline plus taxane combinations should be the recommended first-line treatment for symptomatic patients and for those with rapidly progressing disease.

### 1.1. Optimising therapy for MBC

Patients who have been pre-treated with anthracyclines generally receive either monotherapy with taxanes

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(e.g., docetaxel, paclitaxel) or a combination regimen consisting of a taxane added to an antimetabolite (e.g., gemcitabine, capecitabine). In the majority of trials, such combination regimens have led to a significant prolongation of overall survival compared with taxane monotherapy. However, there remains a need to further optimise combinations in terms of efficacy and/or toxicity. For example, docetaxel plus capecitabine at its standard dosage is an efficacious, yet toxic combination, whereas the combinations of gemcitabine plus docetaxel and gemcitabine plus paclitaxel are efficacious with limited toxicity. Preclinical and clinical data relating to gemcitabine plus taxane combinations are reviewed below.

## 2. Preclinical rationale for combining gemcitabine with a taxane

*In vitro* preclinical studies have demonstrated synergistic efficacy between gemcitabine and the taxanes. For instance, synergistic efficacy is evident between gemcitabine and paclitaxel when the taxane is administered first *in vitro* in MCF-7, MDA-MB-231 and MDA-MB-468 cell-lines [3]. There is also synergy between gemcitabine and docetaxel when the taxane is administered prior to gemcitabine in human gastric cancer cell lines [4].

## 3. Clinical evidence for combining gemcitabine with a taxane

Synergy was also observed *in vivo* in a phase II study. Alexopoulos et al. treated fifty MBC patients with progressive or stable disease on docetaxel with four or more 21-day cycles of gemcitabine 900 mg/m$^2$ (on days 1 and 8) and docetaxel 100 mg/m$^2$ (on day 8) [5]. Responses were achieved in 46% of patients (three complete responses and 20 partial responses) [5].

In the seven studies of gemcitabine plus paclitaxel, overall response rates (ORRs) ranged from 40% to 71%, and time to disease progression (TtDP) ranged from 7.2 to 16.6 months. In the thirteen studies of gemcitabine plus docetaxel, ORRs ranged from 33% to 79% and TtDP ranged from 5.7 to 13.6 months. These combinations have been further evaluated in phase III trials.

### 3.1. Phase III study of gemcitabine plus paclitaxel

In a study by Albain et al., patients who had previously received neoadjuvant therapy for treatment of MBC with an anthracycline were randomised to either paclitaxel 175 mg/m$^2$ for 3 hours (day 1, every 21 days) plus gemcitabine 1250 mg/m$^2$ (day 1, 8, every 21 days) or paclitaxel 175 mg/m$^2$ for 3 hours (day 1, every 21 days) [6]. ORRs were impressive and significantly better in the gemcitabine plus paclitaxel arm than in the paclitaxel monotherapy arm (40.8% [95% confidence interval (CI): 34.9–46.7%] vs. 22.1% [95% CI: 17.1–27.2%]; P < 0.0001). Progression-free survival (PFS) data were also encouraging, significantly favouring the gemcitabine plus paclitaxel combination over paclitaxel alone (hazard ratio [HR] = 0.65 [0.524–0.805]; P < 0.0001) (Figure 1) [6].

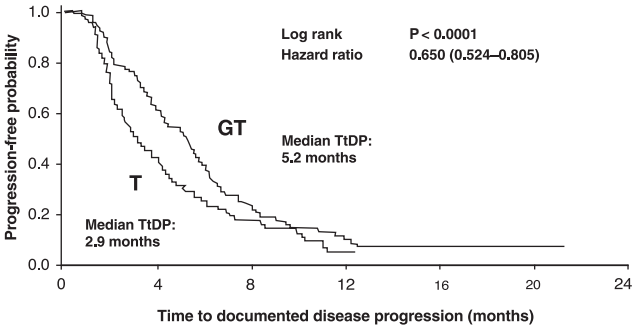


**Fig. 1 – Comparison of time to disease progression (TtDP) between treatment arms [6]. T, paclitaxel; GT, gemcitabine plus paclitaxel.**

Furthermore, the interim overall survival analysis demonstrated that the combination group had a median overall survival significantly better than the paclitaxel monotherapy group (18.5 months vs. 15.8 months (HR = 0.78 [0.63–0.96]; P = 0.018)). Patients with a Karnofsky performance score (KPS) greater than 90 had an HR of 0.57 (95% CI: 0.45–0.72; P < 0.0001) [6].

The efficacy benefits of gemcitabine plus paclitaxel for treatment of MBC did not appear to be outweighed by adverse events. With respect to haematological toxicity, patients had a comparable incidence of anaemia events (6% vs. 2% for grade III and 1% vs. <1% for grade IV) and thrombocytopenia (5% vs. 0 for grade III and <1% vs. 0 for grade IV) between treatment arms. However, neutropenia was more pronounced in the combination arm (31% vs. 4% for grade III and 17% vs. 7% for grade IV), but this was not found to be clinically relevant. Red blood cell transfusions were also more frequent in the combination arm (10% vs. 4%) but not viewed as problematic. Non-haematological toxicity did not appear to be a major issue, with grade III toxicity similar in both arms. Grade III toxicity in the gemcitabine plus paclitaxel and paclitaxel arms was 5% vs. 4% for sensory neuropathy, 2% vs. <1% for motor neuropathy, 2% vs. 2% for emesis, 6% vs. 1% for fatigue, 3% vs. 2% for diarrhoea and 2% vs. 0% for dyspnoea [6] without any clear-cut pulmonary toxicity occurring in either treatment arm.

In addition, those patients receiving the gemcitabine plus paclitaxel combination had an improved quality of life as measured by the Rotterdam symptom checklist, and a significant increase from baseline score after five and six cycles of chemotherapy. This was not the case in patients who received paclitaxel alone [7]. Overall, patients treated with the gemcitabine plus paclitaxel combination benefited from a higher response and improved PFS, overall survival and quality-of-life score.

### 3.2. Docetaxel plus gemcitabine versus docetaxel plus capecitabine

In a randomised phase III trial of women with anthracycline-pretreated MBC, patients were given a combination of docetaxel 75 mg/m$^2$ (day 1) plus gemcitabine 1000 mg/m$^2$ (day 1, 8) for 21 days or docetaxel 75 mg/m$^2$ (day 1) plus capecitabine 1250 mg/m$^2$ twice daily (days 1–14) for 21 days [8]. The patients were stratified according to the following prognostic factors: first- or second-line treatment for MBC, presence or absence of visceral disease, KPS and prior adjuvant taxane therapy. The primary objective was to evaluate PFS; secondary objectives were analyses of ORR, time-to-treatment-failure (TtTF), toxicity, overall survival and quality of life. Interestingly, PFS was similar in both the docetaxel plus gemcitabine and docetaxel plus capecitabine arms, both at 6 months (59% vs. 62%) and at 12 months (20% vs. 23%), and the overall median PFS was identical (35 weeks). These data were mirrored by the fact that patients in both arms had identical ORRs (32%; P = 0.9332); median TtTF was almost identical (19 vs. 18 weeks; P = 0.5056), while median response duration was longer, but not statistically significant, in the docetaxel plus capecitabine arm (36 vs. 42 weeks; P = 0.3131) [8].

Toxicity was considerably lower in the docetaxel plus gemcitabine arm with 13% of patients having to discontinue treatment due to drug-related adverse events versus 28% of patients in the docetaxel plus capecitabine arm. The main and expected toxicities leading to discontinuation were hand–foot syndrome (<1% vs. 9%) and mucositis (0% vs. 2%) for docetaxel plus gemcitabine versus docetaxel plus capecitabine treated patients, respectively. Diarrhoea, abdominal pain, peripheral neuropathy, neutropenia, leukopenia with capecitabine dosed at 1250 mg/m$^2$ twice daily, and other problems were similar in both arms. Thus, the docetaxel plus capecitabine arm was more toxic though both arms had similar efficacy [8].

### 3.3. Three-arm combinational study

In a phase II, three-arm study of gemcitabine plus taxane combinations for treatment of MBC, 210 mostly anthracycline pre-treated patients were randomised to receive either gemcitabine 1250 mg/m$^2$ (day 1, 8) plus paclitaxel 175 mg/m$^2$ (day 1), every 21 days (GP1 arm), gemcitabine 1000 mg/m$^2$ (day 1, 8) plus paclitaxel 100 mg/m$^2$ (day 1, 8), every 21 days (GP2 arm), or gemcitabine 1000 mg/m$^2$ (day 1, 8) plus docetaxel 40 mg/m$^2$ (day 1, 8), every 21 days (GD arm) [9]. Results showed little difference between GP1, GP2 and GD arms in respect to ORR (49% vs. 52% vs. 52%, respectively), median TtTF (6.3 vs. 5.5 vs. 6.5 months, respectively) and median TtDP (7.5 vs. 7.0 vs. 7.4 months, respectively). Thus, on combining gemcitabine with either paclitaxel or docetaxel, there was little risk of compromising efficacy for treatment of MBC on selecting one combination over the other. For toxicity, neutropenia (grade IV: 18% vs. 18% vs. 31%) was high in all three treatment arms, respectively, and potentially problematic in the docetaxel plus gemcitabine arm; thrombocytopenia was not pronounced in any treatment arm [9].

## 4. Sequential versus concomitant treatment with gemcitabine and taxanes

One of the most important unanswered questions regarding treatment of MBC with a taxane and gemcitabine is whether sequential therapy is preferable to concomitant treatment. CECOG has recently completed a trial (BC 1.3.002) of anthracycline pre-treated patients. TtDP was the primary endpoint. In the concomitant arm, gemcitabine 1000 mg/m$^2$ (day 1, 8) plus docetaxel 75 mg/m$^2$ (day 8) delivered every 22 days (for eight cycles) was compared with sequential administration of docetaxel 100 mg/m$^2$ (day 1) every 22 days (for four cycles), followed by gemcitabine 1250 mg/m$^2$ (day 1, 8) every 22 days (for four cycles). The toxicity analysis data should be available by mid-2007.

## 5. Increase in gemcitabine dose or dose density

One of the main considerations for optimising gemcitabine combination regimens is whether to increase the dose or dose density. Although the conventional dosing schedule can decrease tumour burden and the number of tumour cells, several trials have shown that a dose-dense schedule can achieve a greater and possibly more rapid reduction in tumour burden, and without the risk of tumour cell regrowth (Figure 2).

Data from trials have suggested that increasing the dose or dose density of gemcitabine-based chemotherapy results in higher response rates; specifically, in gemcitabine plus docetaxel combinations response rates were found ranging from 59% to 75% [10–12], and for gemcitabine plus paclitaxel combinations rates of 40% to 71% were seen [13,14] (Table 1) .

### 5.1. Bi-weekly combinations

Pelegri et al. investigated the optimisation of a gemcitabine plus taxane combination by using a bi-weekly schedule [11]. Gemcitabine 2500 mg/m$^2$ (q14 d) plus docetaxel 65 mg/m$^2$ (also q14 d) was evaluated in 48 patients with untreated MBC, leading to very positive results: an ORR of 75% (95% CI: 60–86%) (36/48 patients), a median TtDP of 10.7 months, and a median survival of 32.2 months. Neutropenia (44%) was the predominant grade III/IV haematological toxicity, and asthenia (15%) the predominant non-haematological grade III (but rarely grade IV) toxicity [11].

Another trial, by Colomer et al., used gemcitabine 2500 mg/m$^2$ plus paclitaxel 150 mg/m$^2$ delivered bi-weekly in 43 untreated MBC patients [14]. The ORR was

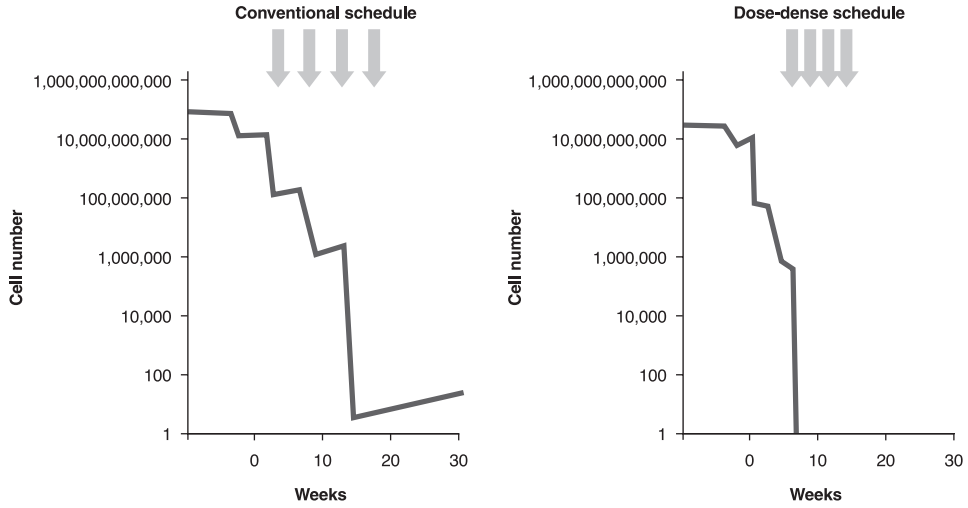


**Fig. 2 – Comparative reduction in tumour cell growth over time between conventional and dose-dense schedules.**

**Table 1 – Treatment schedules and response rates on increasing the dose or dose density in gemcitabine plus taxane combinations [a]**

| Investigator | Dose | n | RR% (CR) | Comments |
|---|---|---|---|---|
| Kornek et al. [10] | G 1.5, D 50 | 34 | 59% | TtDP: 7 months |
| | (d1,15) q 28 | | | Neurotoxicity |
| Pelegri et al. [11] | G 2.5, D 65 | 48 | 75% (17) | TtDP: 10.7 months |
| | (d1,15) q 28 | | | Haematological toxicity, asthenia, transaminase |
| Mavroudis et al. [12] | G 1.5, D 65 | 52 | 59% (13) | TtDP: 10.9 months |
| | (d1,15) q 28 | | | Haematological toxicity, asthenia |
| Sanchez-Rovira et al. [13] | G 2.5, P 135 | 52 | 40% (5) | TtDP: 7.8 months |
| | (d1,15) q 28 | | | Fatigue, neurotoxicity, haematological toxicity |
| Colomer et al. [14] | G 2.5, P 150 | 42 | 71% (10) | TtDP: 14.5 months |
| | (d1,15) q 28 | | | Haematological toxicity |

[a] Abbreviations: G, gemcitabine; D, docetaxel; P, paclitaxel; RR, response rate; CR, complete response; TtDP, time to disease progression.

71% (30 patients), with 11 patients (26%) achieving a complete response. Overall toxicity was low, with grade III neutropenia occurring in 13% of patients and grade IV in 17% of patients; other grade III toxicities occurred in <5% [14].

Since the neutropenic toxicity was mainly non-febrile in nature, this bi-weekly combination could be an acceptable choice for future trials of combination therapy. Currently, two randomised trials are also under way in which bi-weekly gemcitabine plus taxane schedules are being compared with standard gemcitabine plus taxane schedules (Figure 3).

## 6. Combinations with trastuzumab or bevacizumab

A further potential option for optimising combination chemotherapy is to incorporate a molecular-targeting agent such as trastuzumab into the regimen. The impressive efficacy of trastuzumab in patients with human epidermal growth factor receptor (HER)2-over-expressing breast cancer is well known, but the interaction between trastuzumab and other drugs should be considered. For instance, an additive effect is achieved when paclitaxel is combined with trastuzumab, whereas synergistic efficacy is the result on combining trastuzumab with platinum salts, docetaxel or gemcitabine [15]. These synergistic trastuzumab doublet combinations are promising and may provide the best option available at present for patients who have HER2-over-expressing breast cancer.

### *6.1. Trastuzumab triplet combinations*

The efficacy of trastuzumab in triplet combinations has been investigated in a number of trials [16–18]. One trial investigated a triplet combination in 42 patients with evaluable MBC. The schedule consisted of paclitaxel 175 mg/m$^2$ (day 1) with gemcitabine 1200 mg/m$^2$ (day 1, 8) and trastuzumab 4 mg/kg for week 1, then 2 mg/kg weekly thereafter, every 21 days, for a maximum of

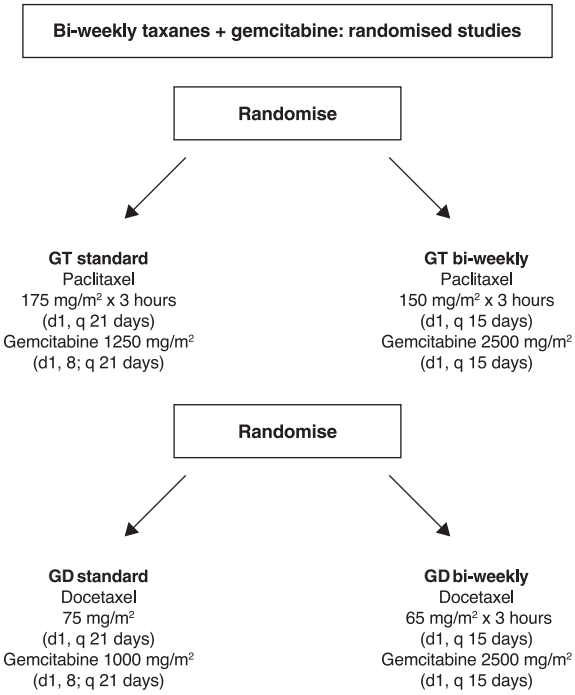


**Fig. 3 – Schedules of standard versus bi-weekly gemcitabine plus taxane regimens. G, gemcitabine; T, paclitaxel; D, docetaxel.**

six cycles until disease progression. The eligibility criteria were HER2-over-expression, as assessed by immunohistochemistry (2+ or 3+) or fluorescence *in situ* hybridisation, a normal left ventricular ejection fraction and no prior chemotherapy. Results showed an impressive ORR of 62%, a complete response in 9% of patients, and, importantly, a median TtDP of 196 days. Median overall survival has not yet been reached, and analysis is ongoing [16].

The multicentre phase II study by Colomer et al. also tested paclitaxel and gemcitabine (both administered bi-weekly) together with trastuzumab (administered weekly) in a triplet combination as first-line treatment for MBC in 27 evaluable HER2-positive patients [17]. The endpoint of the trial was an increase in response rate from 42% (seen with gemcitabine plus paclitaxel in previous trials in this patient group) to $\geqslant$66%. Results recently reported were promising for this combination, with an ORR of 78% (95% CI: 58–91%), seven complete responses, 14 partial responses, and three patients each with stable disease and progressive disease [17].

Finally, another interesting novel molecular-targeting agent that has been tested in doublet and triplet combinations is bevacizumab. This has been combined with paclitaxel with or without gemcitabine in a randomised phase II trial that opened recently, having recruited one patient to date. The treatment schedule consists of paclitaxel (90 mg/m$^2$) dosed weekly plus bevacizumab (10 mg/m$^2$) dosed bi-weekly and gemcitabine (1500 mg/m$^2$) also dosed bi-weekly.

## 7. Conclusion

Taking all of these trials data into account, some impressive results have been achieved combining gemcitabine with a taxane. Gemcitabine plus paclitaxel has shown very good clinical efficacy, particularly with respect to response rates, TtDP and overall survival. Another combination, gemcitabine plus docetaxel, also constitutes a valuable and effective therapeutic option. Undoubtedly, optimisation of these regimens lies in evaluating treatment schedules that have an increased dose and dose density of gemcitabine. Moreover, combinations with targeted treatment modalities show promising preliminary data, with results from ongoing phase II and phase III trials eagerly awaited.

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