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# What is the best schedule for administration of gemcitabine-taxane?

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Until recently, standard adjuvant chemotherapy for metastatic breast cancer (MBC) consisted of anthracycline-based regimens, followed by a taxane. However, data suggest that taxane-based combinations can be more effective than taxanes alone for the second part of treatment. Synergy between paclitaxel and gemcitabine was demonstrated in vitro when paclitaxel was followed by gemcitabine. Dose-dense regimens administered every 2 weeks are more effective than standard 3 weekly regimens. In a phase II study, gemcitabine plus paclitaxel every 2 weeks as first-line chemotherapy of MBC was associated with an overall response rate (ORR) of 71%. Women with HER2 ECD-positive tumours have a poor ORR (40%) to first-line chemotherapy. The addition of trastuzumab to dose-dense paclitaxel-gemcitabine as first-line chemotherapy in women with HER2-positive MBC was associated with a dramatic increase in ORR to 78%, with no serious toxicity observed. Two phase III clinical trials of gemcitabine-paclitaxel as adjuvant chemotherapy in women with histologically-confirmed MBC are currently underway. Preliminary data show that this drug combination is well-tolerated, and the efficacy results are eagerly awaited.


## Introduction

Standard polychemotherapy management of metastatic breast cancer (MBC), consisting of anthracycline- and taxane-based regimens, is associated with high levels of drug-related toxicity and many women often fail to complete the correct course of treatment. Sequential administration of these cytotoxic drugs is associated with significantly lower toxicity than administering the drugs concurrently and in most oncology departments standard therapy for MBC now consists of anthracycline-based combinations, such as doxorubicin plus cyclophosphamide, followed by a taxane. Several recent studies have suggested that taxanes alone are not as effective as taxanes given in combination with another cytotoxic drug in MBC patients [1,2]. In one phase III study of women with anthracyline-pretreated MBC, docetaxel plus capecitabine was associated with a high overall response rate (ORR: 42% vs. 30%, respectively, $p = 0.006$) and longer time to disease

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progression (TTP) (hazard ratio (HR) = 0.652, 95% CI: 0.545–0.780; median TTP: 6.1 vs. 4.2 months, p = 0.0001) compared with docetaxel administered alone [1]. Albain et al. also demonstrated increased efficacy of combination therapy when paclitaxel-gemcitabine was compared with paclitaxel alone in 529 MBC patients treated with prior (neo)adjuvant anthracycline chemotherapy (ORR: 39% vs. 26%, respectively, p = 0.0007; median TTP: 5.4 vs. 3.5 months, respectively, p = 0.0013) [2]. Gemcitabine-paclitaxel offered a significant survival benefit over paclitaxel alone (HR = 0.775, 95% CI: 0.627–0.959; median overall survival (OS): 18.5 vs. 15.8 months, respectively) when administered every 3 weeks until disease progression. One-year survival was 70.7% for gemcitabine-paclitaxel (65.1–76.3%) compared with 60.9% (54.8–66.9%) for paclitaxel alone (p = 0.019) [2].

Most treatment protocols used clinically for the treatment of MBC currently require drug administration every 3 weeks. However, more frequent administration of anticancer drugs has been shown to increase the rate of death of cancer cells [3]. Recent attention has focused on the modification of drug delivery regimens in an attempt to improve the efficacy of chemotherapy. Most of these studies have evaluated dose-dense or accelerated-intensified chemotherapy, involving the administration of cytotoxic drugs every 2 weeks rather than every 3 weeks.

## Dose-dense schedules in MBC

Dose-dense schedules have been compared with standard chemotherapy regimens for a number of different antitumour drug combinations, with variable results. Some investigators reported that the efficacy of accelerated dose-intensified primary chemotherapy with cyclophosphamide, epirubicin plus 5-fluorouracil (CEF), with G-CSF support, was not significantly different to standard 3 weekly regimens in MBC [4,5], whereas others demonstrated significantly increased activity and efficacy of accelerated-intensified treatment regimens [6]. In this latter, randomised trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination adjuvant chemotherapy in 2005 women with node-positive breast cancer conducted by Cancer and Leukaemia Group B, Citron et al. reported a clear survival benefit with accelerated administration of doxorubicin (60 mg/m$^2$), paclitaxel (175 mg/m$^2$) and cyclophosphamide (600 mg/m$^2$), with filgrastim support, every 2 weeks compared with 3 weekly regimens in terms of disease-free survival (DFS) (risk ratio (RR) = 0.74, p = 0.01; OS: RR = 0.69, p = 0.013) [6]. Four-year DFS was 82% with the dose-dense regimen compared with 75% for the standard administration schedule. There was no significant difference in DFS or OS when the drugs were administered concurrently or sequentially. Furthermore, tolerability was superior with the dose-dense regimen and severe neutropenia was observed less frequently than with chemotherapy administered conventionally [6].

A metaanalysis of studies which have investigated this approach has demonstrated a tendency in favour of accelerated chemotherapy compared with chemotherapy administered once every 3 weeks in advanced breast cancer (Fig. 1) [4].

The conflicting results obtained from these studies may be due to the fact that the dose-dense regimens used were based on compression of existing regimens that were originally designed to be administered every 3 weeks. Furthermore, in nearly all studies compression of the dosing schedules required growth factor support. Specifically designed biweekly, dose-dense regimens are now used routinely in patients with Hodgkin's disease (ABVD, CHOP) and colorectal carcinoma (FOLFOX (de Gramont's), FOLFIRI) and it is likely that these regimens are so successful because they can deliver a very large amount of drugs. Amelioration of the efficacy of chemotherapy in MBC might be possible if treatment regimens involving biweekly administration of chemotherapy are designed from scratch rather than being adapted from existing 3 weekly regimens. Several biweekly gemcitabine-based regimens have now been designed in this way and evaluated in phase I, II and III trials in women with MBC and other solid tumours.

## Phase I dose-dense studies with gemcitabine

A number of phase I studies have been carried out to evaluate the efficacy of biweekly administration of gemcitabine alone or in combination with paclitaxel, docetaxel and vinorelbine in patients with refractory or advanced solid tumours [7–10]. These studies demonstrated favourable efficacy and safety with gemcitabine-containing regimens administered repetitively on a 2 weekly schedule, the recommended dose of gemcitabine (3000–5700 mg/m$^2$ every 2 weeks) and accompanying drugs in most of these studies was extremely high.

Based on the results of these phase I trials, we established a dose-dense schedule of gemcitabine-