RESEARCH ARTICLE

A phase 2 open-label study of carboplatin in combination with gemcitabine as a dose-dense schedule in patients with locally advanced or metastatic breast cancer that are resistant to anthracyclines and taxanes [version 1; peer review: 2 approved with reservations]

Christopher Mansbridge^{1,2}, Peter Simmonds^{1,2}, Nicholas Murray³, Andrew Davies ^{1,2}, Louise Stanton⁴, Fay Chinnery ⁴, Caroline Archer⁵, Peter Barrett-Lee⁶, Tamas Hickish ⁷, Simon Crabb^{1,4}

¹University Hospital Southampton NHS Foundation Trust, Southampton, UK

²Cancer Sciences, University of Southampton, Southampton, UK

³Royal Adelaide Hospital, Adelaide, Australia

⁴Southampton Clinical Trials Unit, University of Southampton, Southampton, UK

⁵Queen Alexandra Hospital, Portsmouth Hospitals NHS Trust, Portsmouth, UK

⁶Velindre Cancer Centre, Velindre NHS University Trust, Cardiff, UK

⁷Royal Bournemouth Hospital, The Royal Bournemouth and Christchurch Hospitals NHS Foundation Trust, Bournemouth, UK

v1 First published: 06 Jan 2020, 9:4
<https://doi.org/10.12688/f1000research.21804.1>

Latest published: 06 Jan 2020, 9:4
<https://doi.org/10.12688/f1000research.21804.1>

Abstract

Background: Anthracycline- and taxane-based regimens form the mainstay of chemotherapy treatment in metastatic breast cancer. In patients who develop resistance to these agents, management options are limited and there is no standard of care. Thus, investigation into other chemotherapeutic agents is warranted.

Methods: In this non-randomised prospective trial, patients with human epidermal growth factor 2 (HER-2)-negative locally advanced or metastatic breast cancer that were anthracycline- and taxane-resistant were treated with carboplatin at a dose equivalent to an area under the concentration-time curve of 4.5 mg/ml.min on day 1 and gemcitabine 1500 mg/m² on day 2 of every 2-week cycle. The primary end point was overall response rate.

Results: A total of five patients were enrolled prior to early termination due to difficulty in recruitment. The principal reason for recruitment difficulty was mandating anthracycline and taxane pre-treatment and HER-2 negativity. One patient had a complete response, one had a partial response, one had stable disease and two had progressive disease. Grade 4 neutropenia occurred in two

Open Peer Review

Approval Status

	1	2
version 1
06 Jan 2020	view	view

1. **Lubna N. Chaudhary** , Froedtert and Medical College of Wisconsin, Milwaukee, USA

2. **Caroline Hamm** , Western University, Windsor, Canada

Any reports and responses or comments on the article can be found at the end of the article.

patients.

Conclusions: In this patient population, inclusion criteria that are too stringent may result in difficulties reaching recruitment targets.

Carboplatin in combination with gemcitabine appears to be a safe option for treatment of patients with locally advanced or metastatic breast cancer. Due to the small sample size, it is not possible to draw firm conclusions regarding efficacy from this trial.

Registration: EU Clinical Trials Register ID [2005-005164-83](#), registered on 10 April 2006.

Keywords

Metastatic breast cancer, carboplatin, gemcitabine, chemotherapy

This article is included in the [Oncology](#) gateway.

This article is included in the [All trials matter](#) collection.

Corresponding author: Fay Chinnery (f.chinnery@soton.ac.uk)

Author roles: **Mansbridge C:** Writing – Original Draft Preparation; **Simmonds P:** Investigation; **Murray N:** Conceptualization, Methodology, Supervision; **Davies A:** Conceptualization, Methodology, Supervision; **Stanton L:** Formal Analysis, Methodology; **Chinnery F:** Writing – Review & Editing; **Archer C:** Investigation; **Barrett-Lee P:** Investigation; **Hickish T:** Investigation; **Crabb S:** Conceptualization, Methodology, Supervision

Competing interests: No competing interests were disclosed.

Grant information: The study was funded by Eli Lilly (Lilly study code: B9E-BP-0469).

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Copyright: © 2020 Mansbridge C *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

How to cite this article: Mansbridge C, Simmonds P, Murray N *et al.* **A phase 2 open-label study of carboplatin in combination with gemcitabine as a dose-dense schedule in patients with locally advanced or metastatic breast cancer that are resistant to anthracyclines and taxanes [version 1; peer review: 2 approved with reservations]** F1000Research 2020, 9:4 <https://doi.org/10.12688/f1000research.21804.1>

First published: 06 Jan 2020, 9:4 <https://doi.org/10.12688/f1000research.21804.1>

Introduction

Breast cancer is the most prevalent cancer in women, with over 1.5 million cases diagnosed annually worldwide¹. Of these patients, 20 to 50% will develop metastatic disease², with which only 25% will survive to 5 years³. Anthracycline- or taxane-based regimens form the mainstay of chemotherapy treatment in metastatic breast cancer; however, after failure of these first-line therapies, management of progressive disease is difficult and response rates for salvage therapies are as low as 25%⁴⁻⁶. Hence, further investigation into alternative chemotherapy regimens is required.

Gemcitabine is a pyrimidine analogue and antimetabolite drug with proven anti-tumour activity and tolerability in metastatic breast cancer⁷. In addition, gemcitabine is an excellent agent in polychemotherapy, as demonstrated by its potential for synergistic interactions with platinum agents^{8,9}. Gemcitabine has been used in combination with platinum agents extensively in non-small cell lung cancer (NSCLC) with good results¹⁰ and, in this combination, carboplatin appears to be better tolerated than cisplatin, with similar efficacy rates¹¹.

We proposed a prospective phase II trial to assess the efficacy of gemcitabine in combination with carboplatin in patients with human epidermal growth factor 2 (HER-2) negative, locally advanced or metastatic breast cancer that were anthracycline- and taxane-resistant.

Methods

Patient population

Patients with locally advanced or metastatic breast cancer that had previously been treated with anthracyclines and taxanes were eligible to be screened for entry into the study. The protocol was approved by an independent research ethics committee and all patients gave written informed consent prior to enrolment. Research was conducted in accordance with the Good Clinical Practice guidelines. Consent materials and the full protocol are available as *Extended data*¹².

Patients were approached opportunistically within the hospital setting and screened for eligibility by hospital research staff to ensure all inclusion and exclusion criteria were met. Clinicians sought informed consent to enter the trial from a patient only after the patient had received a full explanation of the trial, had read the PIS and had enough time to consider taking part. Data were collected at the investigational site.

Patients were eligible if they had histologically proven HER-2-negative breast cancer and a diagnosis of locally advanced or metastatic breast cancer, and had previously received treatment with an anthracycline and a taxane either as neoadjuvant, adjuvant or metastatic therapy. Patients were not eligible if they had received more than one prior course of chemotherapy for metastatic disease. Prior hormonal or immunotherapy was allowed, provided anti-tumoral hormonal therapy was terminated prior to enrolment. Prior radiotherapy was also allowed, providing <25% of the bone marrow was treated, the

radiotherapy was completed >4 weeks prior to enrolment, the whole pelvis was not irradiated and the patient had recovered from the acute toxic effects. Irradiated lesions were not included as sites of measurable disease.

Patients were required to have at least one measurable site of disease, defined as a lesion that could be accurately measured in at least one dimension as 2 cm or greater with conventional techniques or as 1 cm or greater with spiral CT scan. Palpable disease was acceptable. Where there was a solitary site of recurrence, histological or cytological confirmation was required.

Other eligibility criteria included: age ≥18 years; Eastern Cooperative Oncology Group (ECOG) performance score ≤1; minimal life expectancy of 12 weeks; adequate bone marrow reserve; adequate renal and hepatic function.

Patients were not eligible for enrolment if they: were pregnant, breast-feeding or refused approved contraception if of reproductive potential; had serious medical or psychiatric illness or serious active infection; had a history of a second primary malignancy other than cervical carcinoma *in situ*, nonmelanomatous carcinoma of the skin or other malignancy treated at least 5 years previously with no evidence of recurrence; had NCIC Common Toxicity Criteria (CTC) grade 2 peripheral neuropathy; or intended to start or stop bisphosphonate therapy within 4 weeks of enrolment. Prior administration of gemcitabine, cisplatin or carboplatin, or concomitant anti-cancer treatment was not permitted. Additionally, patients who received cytotoxic chemotherapy within the preceding 21 days or a drug without regulatory approval within the preceding 30 days prior to enrolment were not eligible.

Patient assessment

Within the 2 weeks prior to commencing treatment, pre-trial investigations were performed. These included taking haematological samples for full blood count, serum biochemistry, hepatic function and estimation of glomerular filtration rate by Cockcroft Gault calculation, and performing a computed tomography (CT) scan of the chest, abdomen and pelvis.

Patients were reviewed regularly throughout treatment. Prior to each 2-week cycle, haematological samples were obtained for full blood count, serum biochemistry and estimation of glomerular filtration rate by Cockcroft Gault calculation. In addition, patients were also required to undergo a physical examination and complete an ECOG performance questionnaire and toxicity assessment.

To assess tumour response, CT scanning of the chest, abdomen and pelvis was performed after cycles 3, 6 and 9 (where applicable). The longest diameters of target lesions were recorded (maximum of five lesions per organ and 10 lesions in total). Lesions were selected on basis of their size (lesions with the longest diameter) and suitability for accurate repeated measurements. Response assessment was based on the Response Evaluation Criteria in Solid Tumours (RECIST) criteria and

classified as a complete response (disappearance of all target lesions), partial response (at least 30% decrease in the sum of the longest diameter of target lesions), progressive disease (at least 20% increase in the sum of the longest diameter of target lesions or the appearance of one or more new lesions) or stable disease (neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease). Overall response rate was defined as the proportion of patients exhibiting a complete or partial response at the end of treatment.

Patients were followed up to obtain data on overall survival (time from date of study entry to date of death from any cause), time to progression (time from date of study entry to date of documented progression or death from any cause), duration of response (time from first documented tumour response to the date of disease progression) and time to treatment failure (time from date of study entry to the date of premature discontinuation of study treatment for any reason, or death from any cause, whichever was sooner).

Treatment schedule

All patients received intravenous carboplatin (dissolved in 250ml 5% dextrose) at a dose consistent with a target area under curve (AUC)¹³ of 4.5 mg/ml.min given over 30 minutes on day 1, and intravenous gemcitabine 1500 mg/m² (up to a maximum dose of 2000 mg) at a fixed dose rate (FDR) of 10 mg/m²/min on day 2 of every 2-week cycle. This biweekly schedule has been shown to be possible in NSCLC¹⁴, where a FDR of gemcitabine^{15,16} and preceding gemcitabine dosing with carboplatin¹⁷ both seem to result in greater efficacy. Body surface area was calculated on each patient's actual height and weight at the commencement of treatment.

The target number of treatment cycles was six. Patients received three treatment cycles initially, followed by a CT scan of the chest abdomen and pelvis. Patients without disease progression then received three further treatment cycles. Patients with an ongoing response as demonstrated by a further CT scan after cycle 6 were eligible to be offered an additional three cycles at the investigators' discretion. Study treatment could be discontinued at any point due to: patient request; recurrent grade 3 or 4 treatment-related toxicity despite dose reduction; allergic reaction to a study drug; evidence of disease progression after two or more cycles of treatment; if the patient became pregnant; or if the responsible clinician felt it was not in the patients best interests to continue on study treatment.

Dose adjustments

Doses were modified based on absolute neutrophil counts (ANC), platelet counts and non-haematological toxicity assessments prior to each cycle. Doses of both gemcitabine and carboplatin were reduced to 80% of the starting dose when ANC decreased to <1000/mm³ or after a first episode of uncomplicated febrile neutropenia. After a first episode of febrile neutropenia with hypotension or requiring hospital admission for more than 4 days, or a second episode of uncomplicated febrile

neutropenia, doses were reduced to 60% of the starting dose or treatment was stopped if there was no evidence of response or the patient was not fit for further chemotherapy. Treatment was discontinued after a third episode of uncomplicated febrile neutropenia, or after a second episode of febrile neutropenia with hypotension or requiring hospital admission for more than 4 days.

When platelet counts decreased to <100,000/mm³, cycles were delayed until platelets recovered (>100,000/mm³). After a second episode of thrombocytopenia (<100,000/mm³), doses of both gemcitabine and carboplatin were reduced to 80% of the starting dose. The dose was further reduced to 60% of the starting dose after a third episode. After a first episode of grade 4 thrombocytopenia or thrombocytopenia-related bleeding, doses of both gemcitabine and carboplatin were reduced to 80% of the starting dose; and this was further reduced to 60% of the starting dose after a second episode.

Clinical assessment of non-haematological toxicity was performed prior to each cycle. Doses were reduced to 80% of the starting dose for CTC grade 3 or 4 toxicities, or to 60% of the starting dose for CTC grade 4 toxicities. In patients with pneumonitis grade 2 or greater, gemcitabine was discontinued. Treatments could also be delayed by up to 2 weeks for any reason deemed appropriate for the treating clinician.

Statistical analysis

The primary endpoint was to determine the overall response rate. Secondary endpoints included overall toxicity, overall survival, time to disease progression, duration of response and time to treatment failure.

A two-stage sampling design was employed¹⁸. For the purposes of this study, a response rate of less than 10% (null hypothesis) was considered to yield no advantage over existing therapies. Conversely, a response rate of 30% or greater (alternative hypothesis) was to indicate that the experimental regimen was of interest and warranted further evaluation. In order to reach a power of 0.9, the recruitment target was 35 patients.

Trial registration

The trial was entered into EudraCT on 10-APR-2006 (EudraCT Number: 2005-005164-83); <https://www.clinicaltrialsregister.eu/ctr-search/trial/2005-005164-83/GB>.

Ethics and monitoring

The trial received ethical approval from Southampton & South West Hampshire REC (A) (06/Q1702/46) on 15 June 2006. It received approval from the UK Medicines and Health Care Product Regulatory Agency (MHRA) to be conducted in the UK (MHRA CTA number 11709/0208/001-0002). Southampton Clinical Trials Unit (SCTU), a UK Clinical Research Collaboration-registered CTU, coordinated the trial. Southampton University Hospitals NHS Trust was the sponsor for the trial (email: R&Doffice@suht.swest.nhs.uk).

Results

Recruitment

In total, five patients were recruited from two secondary care sites in the United Kingdom between 2007 and 2008. The study was terminated early due to difficulty in accruing patients in November 2008.

Of the 34 patients screened, 29 (85%) did not meet the entry criteria and only two of the six participating sites were able to recruit patients. The most common reasons for screen failures included patients having had no previous adjuvant chemotherapy (31%) and HER-2 positivity (17%), as shown in [Figure 1](#). Delays were also experienced waiting for local Research and Development departments to approve the study and not returning essential documents in a timely manner. The Trial Steering Committee reviewed the data and concluded that the trial would not complete in a reasonable timeframe. The primary endpoint was evaluated in all patients.

Patient characteristics

The median age of participants was 38 years (range 30 to 72 years), and all five patients were female. Patient characteristics at study entry are shown in [Table 1](#).

Treatment delivery

Gemcitabine and carboplatin were administered intravenously by the Investigator or member of their clinical team to individual patients at the investigational sites. As a result, patient compliance monitoring was ensured. Patients who returned for follow up visits received study drug unless they encountered toxicity problems or their disease had progressed.

The study case report form was monitored by Southampton Clinical Trials Unit trial staff to ensure the gemcitabine and carboplatin doses were administered as scheduled.

The median number of cycles received was six (range 3 to 9 cycles). Two patients received less than 6 cycles, one due to progressive disease and one due to toxicity. One patient received 9 cycles due to a complete response.

Of the received cycles, six doses (21%) of 28 doses of gemcitabine planned were reduced, and 15 doses (54%) delayed. No doses were omitted. The reason for reduction was myelosuppression (thrombocytopenia and anaemia), and the main reason for delay was neutropenia. Likewise, six (21%) of the 28 doses of carboplatin planned were reduced, and 15 doses (54%)

Figure 1. Flow of participants.

Table 1. Baseline characteristics.

Variable	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Age, years	38	46	72	30	35
Sex	Female	Female	Female	Female	Female
ECOG PS	1	1	0	0	0
Histological type	Ductal adenocarcinoma	Ductal	Mammary adenocarcinoma	Ductal adenocarcinoma	High grade DCIS
Baseline target lesions	6	1	1	3	5
Baseline non-target lesions	4	4	1	1	0
Sites of metastatic disease	Lung, lymph node, liver	Liver, lung	Lymph node, lung	Lung	Liver
Oestrogen receptor status	Negative	Positive	Negative	Negative	Negative
Type of neoadjuvant chemotherapy	-	-	-	-	Doxorubicin, cyclophosphamide, epirubicin
Type of adjuvant chemotherapy	Epirubicin + CMF	NEAT trial chemotherapy ¹⁹	FEC	FEC, Docetaxel	Docetaxel
Type of metastatic chemotherapy	Docetaxel	Docetaxel	Docetaxel	-	-
Prior radiotherapy	Yes	Yes	Yes	Yes	Yes
Prior hormonal treatment	Goserelin	Tamoxifen	No	No	Tamoxifen, Goserelin

Abbreviations: ECOG PS, The Eastern Cooperative Oncology Group Performance Status score; CMF, cyclophosphamide, methotrexate and 5-fluorouracil; FEC, 5-fluorouracil, epirubicin and cyclophosphamide

delayed. No doses were omitted. The reason for reduction was myelosuppression (anaemia and neutropenia), and the main reason for delay was neutropenia.

Notably, in three of five of the patients, the protocol was incorrectly followed by the investigating site and, in response to neutropenia, doses of both gemcitabine and carboplatin were delayed rather than reduced.

Efficacy

Of the five patients who completed treatment, one patient achieved a complete response, one patient achieved a partial response, one patient had stable disease and two patients had disease progression. The patient with a complete response was lost to follow-up. All four of the remaining patients died, and the median overall survival was 6.3 months (range 5.0–31.6). The median time to treatment failure was 3.9 months (range 1.8–5.4), and the median time to progression was 4.7 months (range 1.8–31.6). For the patient with a partial response, the duration of response was 4.1 months.

Toxicity

All patients were evaluated for toxicity (Table 2). The predominant toxicities which occurred in all patients were neutropenia and anaemia. One patient developed neutropenic

sepsis and subsequently discontinued treatment. There were no severe non-haematological toxicities.

Discussion

In this study, gemcitabine in combination with carboplatin seemed to be effective in treating a small number of HER-2-negative advanced or metastatic breast cancer patients. The study, however, closed early and did not reach the recruitment target of 35 patients to provide adequate power for statistical analysis. Hence, we are unable to draw firm conclusions regarding the efficacy of this combination from this study.

The major reason for early closure was difficulty in recruitment. It proved difficult to source patients who had had previous chemotherapy, including an anthracycline and a taxane, and who were HER-2 negative and fit to receive further chemotherapy. The entry criteria proved to be too stringent, limiting the number of eligible patients. This is important for future studies to take into consideration because, if using similar criteria, recruitment targets may not be met within a reasonable timeframe.

The response rate seen in this study was 40%. In view of the young study population who had not had a large amount of pre-treatment, a reasonable response rate was expected. There

Table 2. Treatment toxicity per patient.

	CTC grade	
	1/2	3/4
Neutropenia	2 (40%)	3 (60%)
Anaemia	3 (60%)	2 (40%)
Thrombocytopenia	2 (40%)	2 (40%)
Leukopenia	3 (60%)	1 (20%)
Nausea/vomiting	4 (80%)	
Alopecia	3 (60%)	
Fatigue	3 (60%)	
Somnolence	2 (40%)	
Constipation	2 (40%)	
Mucositis	2 (40%)	
Dyspnoea	2 (40%)	
Anorexia	1 (20%)	
Dizziness	1 (20%)	
Cough	1 (20%)	
Sore feet	1 (20%)	
Neck pain	1 (20%)	
Photophobia	1 (20%)	
Erythema	1 (20%)	
Fever	1 (20%)	

Abbreviations: CTC, NCIC Common Toxicity Criteria v3.0

are now several other small phase II studies that have tested the combination of gemcitabine and carboplatin in pre-treated metastatic breast cancer^{20–24}. These trials yielded lower response rates of 30–39%, with times to progression of 4.6–7.0 months. Entry criteria were generally less stringent, for example not requiring patients to be pre-treated with an anthracycline and taxane^{23–25} or including patients with any HER-2 status^{22–24}, which may account for success in accruing patients to these studies.

Significant haematological toxicities were seen in this trial, with all patients developing neutropenia and anaemia, 60% and 40% of which were grade 3/4 respectively. One patient developed grade 4 febrile neutropenia. The proportion of patients developing haematological toxicities was comparable to other phase II studies testing the combination, where febrile neutropenia occurred in 10–15% of patients, grade 3/4 neutropenia in 10–58%, grade 3/4 thrombocytopenia in 9–51% and grade 3/4 anaemia in 10–27%^{20–24}. Non-haematological toxicities were not severe.

In contrast to other phase II studies where gemcitabine has been given at 1000mg/m² on day 1 and 8 of every 3 week cycle^{20–24}, we gave 1500mg/m² on day 2 of every 2 week cycle at a FDR of 10mg/m²/min, after it was suggested this may

be more efficacious in NSCLC^{15,16}. Due to the failure to meet recruitment targets and deviations from the protocol at one centre, further investigation is required to determine the efficacy of this regimen in metastatic breast cancer.

In summary, this study highlights the difficulty in accruing HER-2 negative metastatic breast cancer patients who have been pre-treated with both anthracyclines and taxanes. In addition, although firm conclusions regarding efficacy cannot be made due to insufficient power, this study suggests the combination of gemcitabine and carboplatin is able to be delivered to this patient population and may be efficacious, in line with other phase II studies which have now been conducted.

Data availability

Underlying data

Pseudonymised individual participant data (IPD) within the clinical trial dataset are available for sharing via controlled access by authorised SCTU staff (as delegated to SCTU by the trial sponsor). Data access can be requested via a SCTU Data Release application form (available from <https://www.south-ampton.ac.uk/ctu/about/index.page>); detailing the specific requirements and the proposed research, statistical analysis, publication plan and evidence of research group qualifications. Please email the completed form to the SCTU Data Release Committee Coordinator at ctu@soton.ac.uk.

Data access requests are reviewed against specific eligibility criteria by the SCTU data custodian and key members of the trial team, including a statistician and chief investigator or by an external Independent Review Panel. Decisions about requests are made promptly and usually no more than three months after receipt of request. Responses to all data requests, with a clear rationale for any refusals, will be sent promptly to the data requester.

Extended data

Figshare: A phase 2 open-label study of carboplatin in combination with gemcitabine as a dose-dense schedule in patients with locally advanced or metastatic breast cancer that are resistant to anthracyclines and taxanes. <https://doi.org/10.6084/m9.figshare.11417550.v1>¹².

The following extended data are available:

- GemCarbo Protocol Version 3 08-11-06.pdf
- Patient Informed Consent Form Version 3 08-11-06.pdf

Reporting guidelines

Figshare: TREND Statement for 'A phase 2 open-label study of carboplatin in combination with gemcitabine as a dose-dense schedule in patients with locally advanced or metastatic breast cancer that are resistant to anthracyclines and taxanes'. <https://doi.org/10.6084/m9.figshare.11417550.v1>¹².

Extended data and reporting guidelines are available under the terms of the [Creative Commons Attribution 4.0 International license](#) (CC-BY 4.0).

References

1. Ferlay J, Soerjomataram I, Dikshit R, *et al.*: **Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012.** *Int J Cancer.* 2015; **136**(5): E359–86.
[PubMed Abstract](#) | [Publisher Full Text](#)
2. Lu J, Steeg PS, Price JE, *et al.*: **Breast cancer metastasis: challenges and opportunities.** *Cancer Res.* 2009; **69**(12): 4951–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
3. Howlader N, Noone AM, Krapcho M, *et al.*: **SEER Cancer Statistics Review. 1975–2012.** National Cancer Institute; Bethesda, MD based on November 2014 SEER data submission, posted to the SEER web site, April 2015.
[Reference Source](#)
4. Porikka K, Blomqvist C, Rissanen P, *et al.*: **Salvage therapies in women who fail to respond to first-line treatment with fluorouracil, epirubicin, and cyclophosphamide for advanced breast cancer.** *J Clin Oncol.* 1994; **12**(8): 1639–47.
[PubMed Abstract](#) | [Publisher Full Text](#)
5. Blum JL, Dieras V, Lo Russo PM, *et al.*: **Multicenter, Phase II study of capecitabine in taxane-pretreated metastatic breast carcinoma patients.** *Cancer.* 2001; **92**(7): 1759–68.
[PubMed Abstract](#) | [Publisher Full Text](#)
6. Livingston RB, Ellis GK, Gralow JR, *et al.*: **Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer.** *J Clin Oncol.* 1997; **15**(4): 1395–400.
[PubMed Abstract](#) | [Publisher Full Text](#)
7. Blackstein M, Vogel CL, Ambinder R, *et al.*: **Gemcitabine as first-line therapy in patients with metastatic breast cancer: a phase II trial.** *Oncology.* 2002; **62**(1): 2–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
8. Perez EA: **Gemcitabine and platinum combinations in patients with breast cancer previously treated with anthracyclines and/or taxanes.** *Clin Breast Cancer.* 2004; **4**(Suppl 3): S113–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
9. Peters GJ, Bergman AM, Ruiz van Haperen VW, *et al.*: **Interaction between cisplatin and gemcitabine in vitro and in vivo.** *Semin Oncol.* 1995; **22**(4 Suppl 11): 72–9.
[PubMed Abstract](#)
10. Zatloukal P, Petruzelka L: **Gemcitabine/carboplatin in advanced non-small cell lung cancer.** *Lung Cancer.* 2002; **38**(Suppl 2): S33–6.
[PubMed Abstract](#) | [Publisher Full Text](#)
11. Mazzanti P, Massacesi C, Rocchi MB, *et al.*: **Randomized, multicenter, phase II study of gemcitabine plus cisplatin versus gemcitabine plus carboplatin in patients with advanced non-small cell lung cancer.** *Lung Cancer.* 2003; **41**(1): 81–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
12. Mansbridge C, Simmonds P, Murray N, *et al.*: **A phase 2 open-label study of carboplatin in combination with gemcitabine as a dose-dense schedule in patients with locally advanced or metastatic breast cancer that are resistant to anthracyclines and taxanes.** *figshare.* Journal contribution. 2019.
<http://www.doi.org/10.6084/m9.figshare.11417550.v1>
13. Calvert AH, Newell DR, Gumbrell LA, *et al.*: **Carboplatin dosage: prospective evaluation of a simple formula based on renal function.** *J Clin Oncol.* 1989; **7**(11): 1748–56.
[PubMed Abstract](#) | [Publisher Full Text](#)
14. Mancuso A, Migliorino MR, Martelli O, *et al.*: **A new biweekly schedule of carboplatin and gemcitabine: Phase I feasibility trial in patients with advanced non-small cell lung cancer (NSCLC).** *Proc Am Soc Clin Oncol.* 2004; **22**: 7245.
[Publisher Full Text](#)
15. Tempero M, Plunkett W, Ruiz Van Haperen V, *et al.*: **Randomized phase II comparison of dose-intense gemcitabine: thirty-minute infusion and fixed dose rate infusion in patients with pancreatic adenocarcinoma.** *J Clin Oncol.* 2003; **21**(18): 3402–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
16. Ceribelli A, Gridelli C, De Marinis F, *et al.*: **Prolonged gemcitabine infusion in advanced non-small cell lung carcinoma: a randomized phase II study of two different schedules in combination with cisplatin.** *Cancer.* 2003; **98**(2): 337–43.
[PubMed Abstract](#) | [Publisher Full Text](#)
17. Bajetta E, Stani SC, De Candis D, *et al.*: **Preclinical and clinical evaluation of four gemcitabine plus carboplatin schedules as front-line treatment for stage IV non-small-cell lung cancer.** *Ann Oncol.* 2003; **14**(2): 242–7.
[PubMed Abstract](#) | [Publisher Full Text](#)
18. Simon R: **Optimal two-stage designs for phase II clinical trials.** *Control Clin Trials.* 1989; **10**(1): 1–10.
[PubMed Abstract](#) | [Publisher Full Text](#)
19. Earl HM, Hiller L, Dunn JA, *et al.*: **NEAT: National Epirubicin Adjuvant Trial--toxicity, delivered dose intensity and quality of life.** *Br J Cancer.* 2008; **99**(8): 1226–31.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
20. Nelli F, Moscetti L, Natoli G, *et al.*: **Gemcitabine and carboplatin for pretreated metastatic breast cancer: the predictive value of immunohistochemically defined subtypes.** *Int J Clin Oncol.* 2013; **18**(2): 343–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
21. Maisano R, Zavettieri M, Azzarello D, *et al.*: **Carboplatin and gemcitabine combination in metastatic triple-negative anthracycline- and taxane-pretreated breast cancer patients: a phase II study.** *J Chemother.* 2011; **23**(1): 40–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
22. Chan D, Yeo WL, Tiemsim Cordero M, *et al.*: **Phase II study of gemcitabine and carboplatin in metastatic breast cancers with prior exposure to anthracyclines and taxanes.** *Invest New Drugs.* 2010; **28**(6): 859–65.
[PubMed Abstract](#) | [Publisher Full Text](#)
23. Laessig D, Stemmler HJ, Vehling-Kaiser U, *et al.*: **Gemcitabine and carboplatin in intensively pretreated patients with metastatic breast cancer.** *Oncology.* 2007; **73**(5–6): 407–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
24. Nasr FL, Chahine GY, Kattan JG, *et al.*: **Gemcitabine plus carboplatin combination therapy as second-line treatment in patients with relapsed breast cancer.** *Clin Breast Cancer.* 2004; **5**(2): 117–22, discussion 123–4.
[PubMed Abstract](#) | [Publisher Full Text](#)
25. Andres R, Mayordomo JI, Lara R, *et al.*: **Gemcitabine/capecitabine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes.** *Clin Breast Cancer.* 2005; **6**(2): 158–62.
[PubMed Abstract](#) | [Publisher Full Text](#)

Open Peer Review

Current Peer Review Status: ? ?

Version 1

Reviewer Report 23 May 2022

<https://doi.org/10.5256/f1000research.24035.r135860>

© 2022 Hamm C. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Caroline Hamm

Western University, Windsor, Canada

This is a well-written prospective, multi-centre trial that unfortunately had very poor accrual. Progesterone receptor status is not mentioned and therefore difficult to define the study population. Therefore it is difficult to apply this study to current clinical practice.

It is unfortunate that only 5 patients were accrued to this study. It appears to be a well written study, open at a number of different sites. I agree with the authors that the criteria of use of a prior anthracycline and taxane in the metastatic setting likely restricted accrual. It is unusual that this study accrued fifteen years ago, and the treatment landscape was likely very different then.

The interest in this study would be with the toxicities of this protocol, rather than the efficacy. Was granulocyte colony stimulating factor used? This is important, since most of the delays were related to neutropenia. However, since three of the five patients, the protocol was followed incorrectly, again making it difficult to interpret toxicities and tolerability.

As the authors stated, perhaps the only learning in this protocol is that their eligibility criteria was flawed. This can guide researchers in writing future trials. In view of this, perhaps a Brief Report is more appropriate for this study.

Is the work clearly and accurately presented and does it cite the current literature?

Yes

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a breast cancer medical oncologist whose research focuses triple negative breast cancer, Innovative chemotherapy regimen development for triple negative breast cancer and clinical trials accrual.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

Reviewer Report 27 July 2020

<https://doi.org/10.5256/f1000research.24035.r66468>

© 2020 Chaudhary L. This is an open access peer review report distributed under the terms of the [Creative Commons Attribution License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Lubna N. Chaudhary

Division of Hematology/Oncology, Froedtert and Medical College of Wisconsin, Milwaukee, WI, USA

This is a prospective study to assess efficacy of dose dense carboplatin and gemcitabine regimen in HER2 negative metastatic breast cancer patients. Patient population is not clearly defined. Locally advanced is not clearly defined in eligibility. ER/PR status is not clearly mentioned. It is unclear from Table 1 if the patient population was triple negative since PR status is not mentioned. Also the time to metastatic disease from their adjuvant/neoadj chemo is not clear. Resistance to anthracycline/taxane is not defined. If TNBC, PD-L1 status is not mentioned.

It is unfortunate that the trial was closed due to poor accrual. The likely reason of difficulty in accrual was the mandated prior anthracycline use in metastatic population where anthracycline is not routinely used as first line therapy. Given the very small sample size, we cannot draw any statistically significant conclusions and stats analysis is not applicable. The authors have correctly given descriptive results given n=5. Please consider submitting this as a brief report instead.

Is the work clearly and accurately presented and does it cite the current literature?

Partly

Is the study design appropriate and is the work technically sound?

Yes

Are sufficient details of methods and analysis provided to allow replication by others?

Yes

If applicable, is the statistical analysis and its interpretation appropriate?

Not applicable

Are all the source data underlying the results available to ensure full reproducibility?

Yes

Are the conclusions drawn adequately supported by the results?

Partly

Competing Interests: No competing interests were disclosed.

Reviewer Expertise: I am a breast medical oncologist in an academic medical center with 8+ years of clinical and translational breast cancer research including two investigator initiated clinical trials and grant fundings.

I confirm that I have read this submission and believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard, however I have significant reservations, as outlined above.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research