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Review

The clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pretreated with an anthracycline and a taxane: A systematic review

Jacek Jassem[a], *Christopher Carroll*[b,*], *Sue E. Ward*[b], *Emma Simpson*[b], *Daniel Hind*[b]

[a]*Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland*
[b]*Health Economics and Decision Science, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK*

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ABSTRACT

Introduction: Currently available evidence does not provide definitive guidance regarding the optimal chemotherapy agents and combinations in anthracycline- and taxane-pretreated advanced breast cancer. We performed a systematic review of controlled clinical trials of the cytotoxic agents currently used for this population in Europe: capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles.

Method: A systematic review of randomised (RCT) and non-randomised controlled clinical trials (non-RCTs). The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), adverse events and quality of life (QoL). Six electronic databases and grey literature sources were searched; reference tracking was performed on included publications. A narrative synthesis was conducted: heterogeneity of study design and interventions prevented meta-analysis.

Results: No randomised controlled trial (RCT) found any significant differences between any of the regimens in terms of OS. In terms of PFS, only gemcitabine plus vinorelbine performed significantly better than its comparator, vinorelbine alone. For secondary outcomes, only capecitabine plus bevacizumab had a significantly better outcome than its comparator, capecitabine alone, in terms of ORR. A low quality non-RCT found that both capecitabine monotherapy and a combination of capecitabine plus vinorelbine were significantly more effective than vinorelbine alone in terms of OS and ORR. Across all trials, median OS for these patients typically remained less than 16 months.

Conclusion: The quantity and quality of the available evidence regarding the efficacy of the particular chemotherapy regimens in patients with advanced breast cancer pretreated with an anthracycline and a taxane is extremely limited. New effective therapies are sorely needed in this population.

* *Corresponding author:* Tel.: +44 0 114 2220864; fax: +44 0 114 2724095.
E-mail address: c.carroll@shef.ac.uk (C. Carroll).
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1. Introduction

Chemotherapy constitutes the major treatment option in both early and advanced breast cancer and the most active currently available agents are anthracyclines and taxanes.[1,2] However, both primary and acquired resistance limit the efficacy of chemotherapy in metastatic breast cancer (MBC). Additionally, increased use of anthracyclines and taxanes in adjuvant and neoadjuvant setting restricts their applicability at relapse.[3,4] Until recently, the only cytotoxic agent approved in the USA and Europe in anthracycline- and taxane-pretreated or -resistant tumours was capecitabine. Several other compounds, including gemcitabine, vinorelbine and nanoparticle protein-bound paclitaxel, all administered as either monotherapy or in combination with other cytotoxic agents, have shown some activity in this setting and are used at the physician's discretion.[5,6] Some patients are also treated with paclitaxel or docetaxel, whereas reinstitution of anthracyclines is difficult due to risk of cumulative cardiotoxicity.

As opposed to the use of chemotherapy in neoadjuvant and adjuvant setting, there are very few internationally accepted consensus statements on therapy of MBC.[7,8] In particular, currently available evidence does not allow for definitive guidance regarding the optimal agents or the order they should be administered in anthracycline- and taxane-pretreated or -resistant tumours. To our knowledge, no systematic review of controlled clinical studies has been published assessing the clinical efficacy of chemotherapy regimens for the treatment of MBC in patients who have previously had treatment with an anthracycline and a taxane. This review therefore aims to determine the efficacy of the principal cytotoxic agents currently used in Europe in this setting: capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles. The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), adverse events and quality of life (QoL).

2. Methods

2.1. Search strategy

This review applied standard systematic review methodology.[9] The aim of the search was the comprehensive retrieval of randomised and non-randomised controlled trials of capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles in anthracycline and taxane resistant or pretreated patients with locally advanced or metastatic breast cancer. A search was performed for randomised controlled trials (RCTs) using the Cochrane Central Register of Controlled Trials (CENTRAL) and the American Society of Clinical Oncology (ASCO) conference proceedings, and a search for non-randomised controlled trial evidence (non-RCTs) was conducted using the major medicine and health-related electronic bibliographic databases MEDLINE, EMBASE, CINAHL and the Science Citation Index, as well as the ASCO annual meeting proceedings. Sensitive search strategies using free-text and, where available, thesaurus terms were developed to search the databases. Synonyms relating to the agents, including chemical and brand names (e.g. Xeloda for capecitabine) were combined with synonyms relating to the condition (breast cancer). An example of the complete CENTRAL search strategy is reported in Appendix 1. In addition to the terms used in the CENTRAL search, a range of terms were used for the non-randomised controlled trials search that aimed to restrict search results to the specific population, i.e. patients with MBC undergoing therapy, who have been treated previously with two or more lines of chemotherapy. These included: 'third line', 'previously treated', 'after treatment with', 'pre-treated', 'subsequent therapy' and 'relapsed', in order to capture the appropriate evidence base. An example of the complete Medline search strategy is reported in Appendix 2. This strategy was modified as appropriate for use on the other databases searched. These searches were also supplemented by other methods to identify relevant citations: the references of all included studies were screened, and industry experts and the reference lists of relevant reviews were also consulted for additional citations. The screening process applied the same inclusion criteria for both sets of search results.

2.2. Selection of studies and quality assessment

To be included in the review, primary research studies had to satisfy the following criteria: controlled trials (randomised or non-randomised); locally advanced or MBC female patients aged $\geqslant$18 years who had received prior therapy with an anthracycline and a taxane; treatment with capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel or paclitaxel protein-bound particles either as monotherapy or in combination with each other or other chemotherapeutic agents; any comparator (e.g. placebo or any drug). The primary outcomes for the review were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), toxicity and quality of life (QoL). Date limits were not used on any database in either set of searches. Restriction to English language was applied to the search for RCTs, but otherwise language restrictions were not used on any database. Studies were excluded if they were phase 1 or single-arm studies; if the trial was exclusively conducted in HER2+ patients, or if less than 50% of the trial population had been treated with both an anthracycline and a taxane (thereby reducing the validity of the evidence for this review), or if the intervention was a high-dose chemotherapy regimen.

All citations identified by the search of electronic databases were downloaded into a Reference Manager database and duplicates removed. Titles and abstracts from both searches were assessed against the inclusion criteria by a single reviewer. For quality-control purposes, a double check for appropriate inclusion and exclusion was performed on ten percent of the citations by a second reviewer. In cases where a decision could not be made about inclusion by a reviewer, citations were checked by a second reviewer and disagreements were either resolved by discussion or the full paper was retrieved in order to make a definitive judgement. One reviewer extracted data from the final list of included studies into pre-designed tables, which were piloted on an included study, and appraised the quality of the included studies using a form

based on standard criteria for RCTs[9], and a form based on the Downs and Black checklist for non-RCTs.[10] The aim was to assess issues relating to randomisation and recruitment, comparability of groups, blinding and analysis. Both data extraction and quality assessment were checked by a second reviewer. The quality assessment process was undertaken to afford a basic idea of the respective quality of studies.

2.3. *Data analysis*

For the primary outcomes (OS and PFS) the hazard ratio (HR) was applied as the most appropriate statistic. When possible, the HR and associated variances were extracted directly from the trial publications. If not reported, it was obtained indirectly using the methods described by Parmar et al.[11], using either other available summary statistics or data extracted from published Kaplan–Meier curves. The secondary outcomes (ORR, DR and toxicity) were also extracted, if reported. Numbers of grades 3 and 4 adverse events only are tabulated from each included study, and only events experienced by more than 5% of individuals are reported here; this figure is an arbitrary threshold confirmed after initial assessment of the available evidence. Grades 3 and 4 events are considered to be 'severe', requiring hospitalisation, and are likely or certainly related to the agent(s) being evaluated.[12] These data were not synthesised statistically, but were summarised. Given the low volume of RCT evidence, and the heterogeneity of interventions, meta-analysis was not performed. Instead, a narrative synthesis of the included studies was performed.[13]

3. Results

3.1. *Studies identified*

The combined searches found a total of 2,592 citations. Of the titles and abstracts screened, 303 full papers or abstracts were retrieved and assessed in detail. After checking full papers against the inclusion criteria, 3 RCTs[14–16] and 1 non-RCT[17] were identified that satisfied the inclusion criteria. A fourth RCT[18] was identified by industry experts (this study was not identified by the original searches because the citation had not yet been catalogued on CENTRAL when the searches were performed). As required in the reporting of analyses of controlled trials[19], a QUOROM flow chart describing the process of identifying relevant literature was drawn (Fig. 1). The majority of the excluded articles had a sample population that had not received both anthracyclines and taxanes (usually the sample had not received a taxane), or they did not examine the specified interventions as either monotherapy or in combination. One non-RCT was excluded because exact numbers of patients pre-treated with both an anthracycline and a taxane were not reported, but could not have exceeded 35% of the sample population.[20]

Three RCTs and the 1 non-RCT examined vinorelbine alone or in combination with another agent[15–18] (Table 1). Two trials compared intravenous, single-agent vinorelbine, either versus a combination of gemcitabine and vinorelbine[18] or versus single-agent capecitabine or a combination of vinorelbine and capecitabine.[17] One study compared intravenous vinorelbine plus 5-fluorouracil (5FU) versus intravenous oxaliplatin plus 5FU[16], and one single-agent pegylated liposomal doxorubicin versus vinorelbine or mitomycin C plus vinblastin.[15] One RCT compared the efficacy and safety of single-agent oral capecitabine with a combination of oral capecitabine and intravenous bevacizumab.[14]

In three of the four RCTs, all participants had been pre-treated with both a taxane and an anthracycline, and no data were reported on resistance.[14,16,18] Another trial specifically included women with taxane-refractory breast cancer (defined as disease progression during or within 6 months of the last dose of a taxane-containing regimen for advanced disease), but with no more than 2 months elapsing between

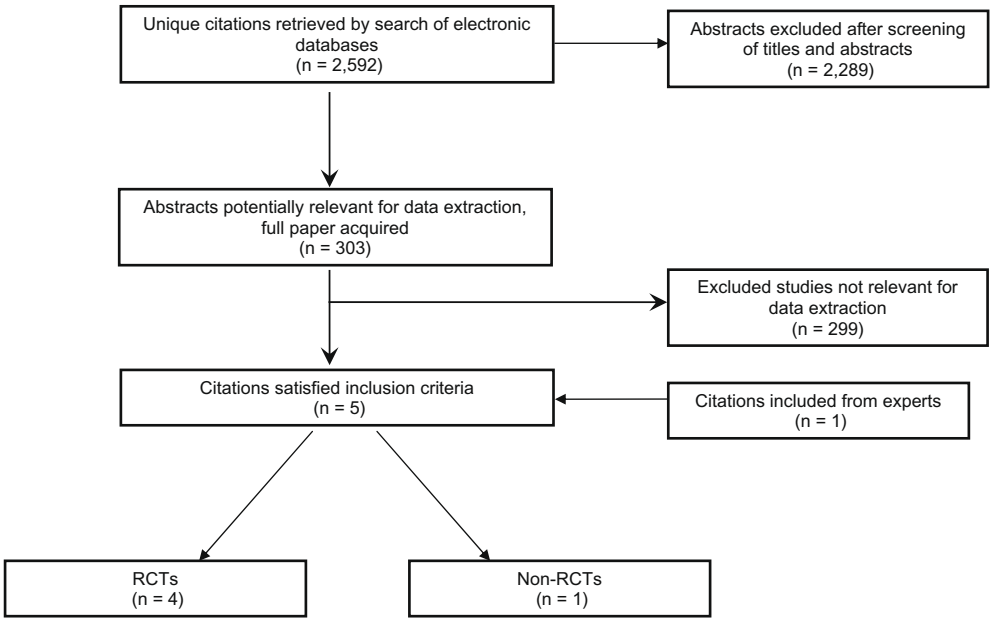

Fig. 1 – QUOROM flow diagram.

Table 1 – Study and sample characteristics.

Study, design, setting	Inclusion criteria	Exclusion criteria	Intervention / comparators Treatment 1 (T1) Treatment 2 (T2)	Median age in years: (range)	Number of prior CT regimens for metastatic breast cancer (%)	⩾3 Metastatic sites
Phase III, multicentre (37 centres), unblinded, randomised controlled trial[18] Spain	• Locally recurrent and metastatic BC • Prior therapy with an anthracycline and a taxane • ⩽2 previous chemotherapy regimens for metastatic disease • Aged ⩾18 years • WHO performance status of ⩽2 • Sufficient bone marrow reserve • Adequate liver and renal function • Estimated life expectancy of 12 weeks • Previous chemotherapy completed ⩾4 weeks prior to treatment	• Pregnant • Breastfeeding • Male • Previous therapy with gemcitabine or vinorelbine or any other therapy ⩽30 days of study enrolment • Active infection • Serious systemic disorder • Previous grade 3–4 neurotoxicity • A second primary malignancy (except in situ cervical cancer or adequately treated non-melanoma skin cancer) • Clinical evidence of brain metastases or blastic bone metastates as the only site of disease	T1: GEM + VIN (IV), *n* = 125 T2: VIN (IV), *n* = 126	T1: 58 (28–82) T2: 57 (35–80)	0 T1: 26 (21) T2: 19 (16) 1 T1: 65 (52) T2: 68 (54) 2 T1: 34 (27) T2: 39 (31)	T1: 27% T2: 33%
Phase III, multicentre (NR), open label, single-blinded, randomised controlled trial[14] USA	• Metastatic BC • Prior therapy with an anthracycline and a taxane • 1–2 Previous chemotherapy regimens for metastatic disease • If there was relapse within 12 months of completing anthracycline or taxane therapy, patients were eligible without any intervening chemotherapy • Bidimensionally measurable disease with ⩾1 lesion measuring ⩾2 cm • Eastern Cooperative Oncology Group (ECOG) performance status of 0 or 1 • Adequate renal, hepatic and haematologic function	• A history or radiographic evidence of Central Nervous System disease • Any other primary malignancy except basal carcinoma of the skin or in situ cervical cancer within 5 years • Major surgery within 4 weeks • Any other tumour therapy within 21 days • A non-healing wound, fracture or infection requiring parenteral antibiotics • Clinically significant cardiovascular disease	T1: CAP (oral), *n* = 230 T2: CAP (oral) + BEV (IV), *n* = 232	T1: 52 (30–77) T2: 51 (29–78)	0 T1: 37 (16) T2: 35 (15) 1 T1: 98 (43) T2: 107 (46) 2 T1: 87 (37) T2: 79 (34) 3–5 T1: 8 (3.5) T2: 11 (4.7)	T1: 50% T2: 49%

Phase III, open label, unblinded, multi-centre (52), randomised controlled trial[15] USA	• Metastatic or locally advanced BC (stage IIIB or IV) • ⩽2 Previous chemotherapy regimens for metastatic disease (last regimen must have included a taxane) • Stable Karnofsky performance status of ⩾60 • At least 1 measurable lesion • Completed baseline HRQOL questionnaire	• Abnormalities in haematological parameters, renal or liver function • Any exposure to one of the experimental drugs within the month prior to the study • Any previous high-dose anthracycline doxorubicin or equivalent therapy • A history of cardiac disease, uncontrolled systemic infection, prior PLD therapy, or radiation to diseased areas within 3 weeks of the study	T1: PLD (IV), $n = 150$ T2: VIN or mitomycin C + vinblastin (IV), $n = 151$ Population with anthracycline resistance: T1: $n = 59$ (39%), T2: $n = 53$ (35%)	T1: 56 (33–87) T2: 56 (30–83)	0 T1: 8 (5) T2: 7 (5) 1 T1: 84 (56) T2: 79 (52) 2 T1: 53 (35) T2: 54 (36) >2 T1: 5 (3) T2: 11 (7)	T1: 26% T2: 34%
Phase II–III, multi-centre (33), randomised controlled trial[16] France	• Relapsing progressive MBC • Prior therapy for metastatic BC with an anthracycline and a taxane • 1–3 Prior MBC chemotherapy regimens • WHO performance status of 0–2 • At least 1 measurable target lesion (RECIST criteria) • Adequate baseline organ function	NR	T1: OXA + 5FU (IV), $n = 68$ T2: VIN + 5FU (IV), $n = 69$	T1: 53 (30–78) T2: 52 (35–73)	⩾2 T1: 31 T2: 26	NR
Multi-centre, retrospective chart review[17] Canada	• Metastatic BC • Pretreatment with anthracyclines and taxanes in an adjuvant or metastatic setting • Treatment with vinorelbine and capecitabine either as single agents or consecutively	• Pretreatment with any other chemotherapy between anthracyclines and taxanes and T1, T2 or T3 • Concurrent therapy with trastuzumab • Any chemotherapy between vinorelbine and capecitabine in the combination therapy sequence	T1: VIN, $n = 45$ T2: CAP, $n = 68$ T3: VIN/CAP consecutively (in either order), $n = 27$ Method of administration NR	T1: 52 ± 11 T2: 53 ± 10 T3: 55 ± 11	NR	T1: 58% T2: 35% T3: 43%

*T1, treatment arm 1; T2, treatment arm 2; T3, treatment arm 3; NR, not reported; VIN, vinorelbine; CAP, capecitabine; GEM, gemcitabine; IV, intravenous; OXA, oxaliplatin; 5FU, 5-fluorouracil; PLD, pegylated liposomal doxorubicin.

taxane failure and study inclusion.[15] A majority (83%) of patients in both treatment groups in this trial had previously received both anthracyclines and taxanes, and 39% and 35% of patients in the pegylated doxorubicin and vinorelbine or mitomycin C plus vinblastin groups, respectively, were anthracycline resistant (defined as disease progression during or within 6 months of the last dose of an anthracycline-containing regimen for metastatic disease).

3.2. *Quality assessment of studies*

Three of the four RCTs were of good but not of high reported methodological quality.[14,15,18] In all of these trials, inclusion and exclusion criteria, and baseline data, were reported; withdrawals were all accounted for and intention-to-treat analyses were performed, and in one trial outcome assessors were blinded.[14] However, in two trials methods of allocation and randomisation were not adequately reported;[14,15] in two trials there was no blinding at all;[15,18] and in one trial the sample size did not satisfy the threshold required by the power calculation for the specified outcome.[18] The fourth RCT was of lower methodological quality, but this trial was published as an abstract only because it was prematurely discontinued due to accrual difficulties.[16] As a result, there was an absence of information on methods of randomisation, allocation and blinding, although inclusion and exclusion criteria, and baseline data were reported and efficacy analysis was conducted using both the intention-to-treat and as-treated approaches.

The quality of the only non-RCT was low.[17] The concealment of treatment allocation and the blinding of assessors were possible, but neither was applied. Withdrawals were neither explained nor accounted for in the analysis (OS was evaluated on only 58% of the total participants who had entered the study) and confounding variables were not considered.

3.3. *Overall survival (OS) and progression-free survival (PFS)*

All trials reported data on OS and PFS (Table 2). Significant differences between study arms were only evident for PFS and OS each in one trial.[17] In terms of PFS, the gemcitabine and vinorelbine combination was significantly more effective than vinorelbine alone ($p = 0.0028$): median PFS for gemcitabine and vinorelbine was 6 months, and for vinorelbine alone was 4 months.[18] In the low quality non-RCT, OS was significantly lower both with vinorelbine monotherapy than cape-

Table 2 – Primary outcomes.

Study quality	Intervention/comparators Randomised (in analysis)	Overall survival (months) median (range)	Progression-free survival (months) median (range)
Good quality RCT[18]	T1: GEM + VIN, $n = 125$ (125)	T1: 15.9 (12.6–19.1); T2: 16.4 (11.6–21.1)	T1: 6.0 (4.8–7.1); T2 = 4 (2.9–5.1)
	T2: VIN, $n = 126$ (126)	HR = 1.04 (0.78–1.39), $p = 0.8046$	HR = 0.66 (0.50–0.88), $p = 0.0028$
Good quality RCT[14]	T1: CAP, $n = 230$ (230) T2: CAP + BEV, $n = 232$ (232)	T1: 14.5; T2: 15.1 HR = 1.12 (0.84–.150), $p = 0.42$[b]	T1: 4.2; T2: 4.9 HR = 0.98 (0.77–1.25), $p = 0.857$
Good quality RCT[15]	T1: PLD, $n = 92$ (92) **$n = 59$ (39%)	*T1: 9.2; T2: 9.5 HR = 0.86 (0.58–1.26), p = NR	*T1: 2.4; T2: 2.7 HR = 0.96 (0.70–1.32), p = NR
	T2: VIN or mitomycin C plus vinblastin, $n = 96$ (96) **$n = 53$ (35%)	**T1: 8; T2: 6.1 HR = 1.05 (0.61–1.83), p = NR	**T1: 2.6; T2: 2.6 HR = 1.14 (0.70–1.83), p = NR
Poor quality RCT[16]	T1: OXA + 5FU, $n = 68$ (68)	T1: 14.6 (10.6–21.7), T2: 16.9 (11.7–20.2)	T1: 4.5 (4.0–5.5), T2: 5.4 (4.4–7.2)
	T2: VIN + 5FU, $n = 69$ (69)	HR = NR; $p = 0.7392$	HR = NR[a], $p = 0.2640$
Poor quality non-RCT[17]	T1: VIN, $n = 45$ (44)	T1: 3.4 T2: 6.1 T3: 12.7	NR
	T2: CAP, $n = 68$ (22)	T1 versus T2 : HR = 0.46 (0.30–0.70), $p = 0.001$ T1 versus T3 : HR = 0.37 (0.22–0.61), $p = 0.001$	
	T3: VIN/CAP consecutively (in either order), $n = 27$ (16)	T2 versus T3 : HR = 0.78 (0.49–1.26), $p = 0.31$	

HR, hazard ratio; NR, not reported; VIN, vinorelbine; CAP, capecitabine; GEM, gemcitabine; IV, intravenous; OXA, oxaliplatin; 5FU, 5-fluorouracil; PLD, pegylated liposomal doxorubicin.

* Results for anthracycline and taxane pretreated sub-group only.

** Anthracycline-resistant population only.

a HR could not be calculated for this report using methods described by Parmar et al.[11] due to insufficient reported data.

b Estimated for this report using methods described by Parmar et al.[11] based on data from the reported Kaplan–Meier curve.

citabine ($p = 0.001$), and with single-agent vinorelbine than the combination of vinorelbine plus capecitabine ($p = 0.001$). However, there was no significant difference in terms of OS between the capecitabine alone and vinorelbine plus capecitabine ($p = 0.31$). No other trial reported any significant differences in terms of PFS or OS between the treatments arms.

One study reported the analyses of both an independent assessment centre and the study investigators;[14] only the former are reported here as they are more robust. In another study, results were reported only for that part of the sample that had been pretreated with both an anthracycline and a taxane (83% in both arms of total sample); separate data were also reported for that part of the sample that was deemed anthracycline resistant.[15]

3.4. *Overall response rates (ORRs)*

All 4 RCTs reported ORR (Table 3), one of which found a significant difference between intervention and comparator: the combination of capecitabine and bevacizumab performed significantly better than capecitabine alone: 19.8% versus 9.1%, $p = 0.001$.[14] DR was reported by 3 RCTs,[14,15,18] and in no trial was there a significant difference between the intervention and comparator arms.

3.5. *Quality of life (QoL)*

Two RCTs and the one non-RCT reported data on QoL. A good quality RCT comparing single-agent capecitabine with the capecitabine and bevacizumab combination found no difference across arms in time to deterioration in QoL (TDQ), as assessed by the Trial Outcome Index ($p = 0.633$).[14] In another good quality RCT, patients taking vinorelbine or mitomycin C plus vinblastin appeared to have lower global QoL than those being treated with pegylated doxorubicin (14.6% versus. 20%), according to the global QoL domain of the European Organisation for Research and Treatment of Cancer – QoL Questionnaire-Core 30,[15] whereas the low quality non-RCT[17] found that vinorelbine alone, rather than vinorelbine and/or capecitabine, might provide greater QoL as the treatment duration was shorter (mean duration of treatment for vinorelbine therapy was 64.4 days, for capecitabine 129.1 days and for vinorelbine plus capecitabine combination 110.5 days). However, treatment duration is an unvalidated proxy for QoL.

Table 3 – Secondary outcomes.

Study	Intervention /comparators	Overall response rate (%)	Duration of response (months) Median (range)	Grades 3 and 4 adverse events	Measure of quality of life (and results)
Martin[18]	T1: GEM + VIN T2: VIN	T1: 36% T2: 26% $p = 0.093$	T1: 4.8 (3.1–6.6) T2: 3.7 (3.0–4.4)	Neutropaenia; T1: 61%; T2: 44%; $p = 0.007$	NR
Miller[14]	T1: CAP T2: CAP + BEV	T1: 9.1% T2: 19.8% $p = 0.001$	T1: 7.6 T2: 5.0	Diarrhoea; T1: 10%; T2: 12% PPE; T1: 24%; T2: 28% Hypertension; T1: 0.5%; T2: 18% Asthenia; T1: 7%; T2: 7% Thrombotic event: T1: 4%; T2: 6%	TOI: T1: 2.9 months, ($n = 176$) T2: 2.9 months, ($n = 194$) $p = 0.633$
Keller[15]	T1: PLD (IV) T2: VIN or mitomycin C plus vinblastin	T1: 10% T2: 12%	T1: 5.7 T2: 6.0	Neutropaenia; T1: 2%; T2: 8% PPE; T1: 19%; T2: 0% Nausea; T1: 0%; T2: 7% Stomatitis; T1: 5%; T2: 0%	Global quality of life domain (EORTC-QLQ-C30) T1: 20%, ($n = 115$) T2: 14.6%, ($n = 117$)
Delaloge[16]	T1: OXA + 5FU T2: VIN + 5FU	T1: 24% T2: 28% $p = 0.5908$	NR	Neutropaenia; T1: 13%;T2: 78%; $p < 0.001$ Mucositis; T1; 12%; T2: 32%; $p = 0.0043$ Neurosensory; T1: 7.5%); T2: 0%; $p = 0.0279$	NR
Verma[17]	T1: VIN T2: CAP T3: VIN/CAP	NR	NR	NR	Mean duration of treatment (days): T1: 65 T2: 129 T3: 110

NR, not reported; VIN, vinorelbine; CAP, capecitabine; GEM, gemcitabine; IV, intravenous; OXA = oxaliplatin; 5FU, 5-fluorouracil; PLD, pegylated liposomal doxorubicin; TOI, trial outcome index (part of the Functional Assessment of Cancer Treatment – Breast (FACT-B) questionnaire); PPE, palmar plantar erythema; EORTC-QLQ-C30 = European Organisation for Research and Treatment of Cancer – Quality of Life Questionnaire-Core 30 (EORTC QLD-C30, version 2.

3.6. Safety

Neutropaenia, nausea and stomatitis or mucositis were the principal grades 3 and 4 adverse events associated with vinorelbine,[15–17] whereas neutropaenia was associated with gemcitabine,[18] and diarrhoea, hand-foot syndrome (HFS) and asthenia with capecitabine.[14] Subjects treated with a combination of gemcitabine and vinorelbine experienced significantly more grades 3–4 events of neutropaenia than those treated with vinorelbine alone (61% versus 44%; $p = 0.007$).[18] Subjects receiving a combination of vinorelbine and 5FU experienced significantly more grades 3–4 neutropaenia and mucositis than those receiving oxaliplatin + 5FU.

4. Discussion

This systematic review demonstrates an astonishing paucity of level 1 clinical evidence for the drugs currently offered in Europe (capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles) for patients with locally advanced or metastatic breast cancer previously treated with both a taxane and an anthracycline. Only 4 RCTs were identified that assessed the efficacy of one or more of the drugs of interest.[14–16,18] One RCT examined capecitabine both as monotherapy and in combination with bevacizumab, whereas the remaining 3 RCTs evaluated vinorelbine, either as combination therapy with gemcitabine or 5FU or as one of the single-agent comparators. In each case, the comparator was different (vinorelbine alone, oxaliplatin and 5FU, and pegylated doxorubicin). The sample sizes in any treatment arm in the RCTs were relatively small and ranged from as little as 68 to a maximum of 232 patients. None was a high quality RCT, but 3 were of relatively good reported methodological quality. The fourth trial was published as an abstract only, limiting its usefulness. No RCT evidence appears to exist on docetaxel, paclitaxel or paclitaxel protein-bound particles in this setting.

The only identified non-randomised controlled trial compared capecitabine and vinorelbine as single agents and in combination. Being a non-RCT, this trial was, by design, of lower quality evidence than the RCTs, but it also had several weaknesses including failure to provide a statistical comparison of participants' baseline data, no explanation for withdrawals and failure to apply intention-to-treat analysis. Similar to RCTs, there were no non-RCTs of gemcitabine, docetaxel, paclitaxel or paclitaxel protein-bound particles either as single agents or in combination.

The RCT evidence currently available demonstrates that neither capecitabine nor vinorelbine was significantly more effective at increasing PFS, OS, DR or ORRs than other single agent or combination regimen in this population. The possible exceptions were the gemcitabine plus vinorelbine and capecitabine plus bevacizumab combinations, which, respectively, appeared to produce better PFS than vinorelbine alone and better ORRs than capecitabine alone. The gemcitabine plus vinorelbine combination was more effective in terms of PFS than vinorelbine alone, although there was no difference in other efficacy outcomes. Both vinorelbine and gemcitabine were found to produce higher numbers of certain grades 3 and 4 adverse events than other drugs, principally neutropaenia, stomatitis and nausea. The most frequent adverse events produced by capecitabine were diarrhoea, hand-foot syndrome and asthenia. The non-randomised trial showed a relative ineffectiveness of single-agent vinorelbine in patients with previous exposure to anthracyclines and taxanes, and the higher frequency of grades 3 and 4 adverse events with this compound. Across all trials, median OS typically remained less than 16 months.

Ideally high quality, randomised, multi-centre, blinded, controlled trials are required that compare optimal doses of particular drugs with optimal doses of reasonable comparators in second or third line of advanced breast cancer. However, such studies are costly and difficult to develop in pretreated populations of patients. As a result, most research so far has been phase II studies or small-scale non-randomised controlled trials comparing particular agents (or combinations thereof) with current service provision in particular countries.

In conclusion, the quantity and quality of the available evidence regarding the efficacy of currently used drugs in patients with locally advanced or metastatic breast cancer previously treated with both a taxane and an anthracycline are extremely limited. A great deal of caution must therefore be exercised when drawing conclusions about the efficacy of these compounds. Additionally, none of these therapies offers apparent clinical benefit over the others. Most importantly, however, currently available cytotoxic agents do not appear to offer an effective means of improving PFS or OS in this population. As a result, the outcome of these patients is poor and there remains a high level of unmet clinical need.

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Conflict of interest statement

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Appendix 1. Example of the complete CENTRAL search strategy

Cochrane Library, Register of Controlled Trials

#1 (Capecitabine) or (Xeloda)
#2 (Gemcitabine) or (Gemzar)
#3 (Vinorelbine) or (Navelbine)
#4 (Docetaxel) or (Taxotere)

#5 (Paclitaxel) or (Taxol)
#6 (Abraxane) or (ABI-007)
#7 (#1 OR #2 OR #3 OR #4 OR #5 OR #6)
#8 (breast)
#9 (#7 AND #8)

Appendix 2. Example of the complete MEDLINE search strategy

Database: ovid MEDLINE(R) <1950 to November week 2 2007>
Search strategy:

1. capecitabine.af. (1299)
2. xeloda.af. (159)
3. vinorelbine.af. (2094)
4. navelbine.af. (312)
5. gemcitabine.af. (4688)
6. gemzar.af. (187)
7. docetaxel.af. (4345)
8. taxotere.af. (700)
9. exp Paclitaxel/(12251)
10. paclitaxel.af. (14368)
11. taxol.af. (4751)
12. (paclitaxel adj3 protein).af. (34)
13. (albumin adj3 paclitaxel).af. (57)
14. abraxane.af. (37)
15. abi-007.af. (37)
16. or/1–15 (22791)
17. exp Breast Neoplasms/(151720)
18. breast cancer.tw. (100933)
19. breast neoplasm$.tw. (747)
20. 17 or 18 or 19 (166292)
21. breast$.tw. (187831)
22. mammar$.tw. (46292)
23. 21 or 22 (222790)
24. cancer$.tw. (629265)
25. neoplasm$.tw. (71195)
26. carcinoma$.tw. (333374)
27. tumour$.tw. (645147)
28. tumour$.tw. (146772)
29. or/24–28 (1342847)
30. 23 and 29 (160038)
31. 20 or 30 (195326)
32. 16 and 31 (4427)
33. third line.tw. (25)
34. third line.tw. (873)
35. previous$ treat$.tw. (10826)
36. after treatment with.tw. (31744)
37. prior chemotherap$.tw. (2263)
38. pre-treated.tw. (3351)
39. relapsing.tw. (11673)
40. relapsed.tw. (15504)
41. subsequent therap$.tw. (725)
42. subsequent chemotherap$.tw. (308)
43. failure.tw. (307708)
44. pretreated.tw. (36540)
45. refractory.tw. (51320)
46. fail$ treatment.tw. (1042)
47. or/33–46 (455475)
48. 32 and 47 (1140)

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