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Review

Capecitabine and vinorelbine in metastatic breast cancer

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ABSTRACT

Background: As anthracyclines and taxanes are frequently used in the adjuvant and first-line metastatic settings, capecitabine and vinorelbine are frequently used as monotherapy and in combination for metastatic breast cancer (MBC). In the absence of comparative, phase III data, retrospective analyses and cross-trial comparisons provide the only indication of the relative efficacy of these options.

Methods: We reviewed studies evaluating the 2 agents alone or in combination in MBC.

Results: We identified 6 capecitabine and 2 vinorelbine phase III trials, numerous phase II monotherapy studies and 35 phase I/II studies exploring capecitabine–vinorelbine combination therapy (1 with trastuzumab in HER2-positive MBC).

Conclusion: For monotherapy, the limited, retrospective comparative evidence supported by consistent prospective data suggests that capecitabine is more effective than vinorelbine. Comorbidities, organ function tolerability, tumour biology and patient characteristics should also inform treatment choice. If combination therapy is deemed clinically appropriate, intravenous vinorelbine with capecitabine may be considered, potentially improving efficacy compared with monotherapy, but at the cost of increased toxicity. Randomised evaluation versus capecitabine monotherapy is ongoing. In contrast, cross-trial comparison suggests that addition of oral vinorelbine to capecitabine adds haematological toxicity without apparently improving efficacy in pretreated MBC. Data from small, single-arm, phase II studies in the first-line setting are more encouraging. In summary, the strongest clinical data support capecitabine monotherapy in the majority of patients. In certain populations, a capecitabine–vinorelbine combination may be appropriate but requires further validation in randomised trials.

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1. Introduction: capecitabine or vinorelbine

Despite the established efficacy of anthracyclines and/or taxanes in the treatment of breast cancer, other agents have demonstrated efficacy in the first- and second-line metastatic setting. Capecitabine, an oral fluoropyrimidine, and vinorelbine, a vinca alkaloid, are used widely in the treatment of metastatic breast cancer (MBC), both as monotherapy and in combination regimens. The decision to give either drug as monotherapy is based on a wide variety of factors, including efficacy in clinical trials, safety profile, patient preference for oral or intravenous (i.v.) therapy, reimbursement issues, local practice guidelines, physician experience, accessibility of the clinic for patient follow-up (e.g. haematological monitoring), treatment setting and exposure to prior therapy.

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1.1. First-line setting

Both agents have been evaluated in extensive clinical trial programmes in MBC, although the use of vinorelbine as first-line therapy is based on evidence from a relatively small dataset and there are few randomised controlled trials of vinorelbine in any setting (Table 1). Use of capecitabine in the first-line setting is supported by results of a randomised, phase III trial in 323 patients, in which capecitabine monotherapy significantly prolonged overall survival (OS) versus classical cyclophosphamide, methotrexate and 5-fluorouracil (CMF).[18] The hazard ratio for OS was 0.72 (95% confidence interval (CI): 0.55–0.94; $p = 0.02$). Median OS was 20–22 months in this and 1 other randomised trial of capecitabine in the first-line setting.[18,19]

The only indication of the relative efficacy of these two agents in the first-line setting comes from a recently reported French retrospective analysis in 96 patients aged ⩾75 years. Median OS was 15.1 months in patients receiving capecitabine versus 10.0 months in patients receiving any other chemotherapy (predominantly vinorelbine [47%] or anthracycline-based therapy [35%]).[20] Median OS among patients receiving vinorelbine (alone or in combination with gemcitabine) was 7.2 months. The median capecitabine starting dose was 1000 mg/m^2 twice daily.

1.2. Pretreated MBC

In subsequent therapy lines, capecitabine has shown consistent efficacy in several studies in anthracycline- and taxane-pretreated MBC (Table 1). Trials in this setting have included single-agent capecitabine in the control arm (versus combinations with bevacizumab,[3] ixabepilone[1,2] and lapatinib in HER2-positive MBC[4]). Based on these robust data, capecitabine is the standard therapy in ongoing trials evaluating sunitinib (alone or in combination with capecitabine), larotaxel and eribulin in anthracycline- and taxane-pretreated MBC.

There are fewer data for vinorelbine monotherapy in pretreated MBC. In a randomised trial conducted in the early 1990s in 179 patients with anthracycline-pretreated MBC, vinorelbine demonstrated a significant OS benefit versus melphalan.[12] Other studies have shown varied results, with response rates (RRs) typically ranging from 12% to 26% (Table 1).

There is no definitive randomised, phase III trial in any setting allowing comparison of the efficacy of vinorelbine versus capecitabine. The European Organisation for Research and Treatment of Cancer (EORTC) planned a randomised trial of capecitabine versus i.v. vinorelbine in patients with anthracycline- and taxane-pretreated MBC, but the preliminary phase II trial assessing activity of the 2 agents was stopped after accrual of only 47 of 72 planned patients due to poor recruit-

Table 1 – Summary of phase II/III trials (n ⩾ 50) evaluating capecitabine or vinorelbine as monotherapy in pretreated metastatic breast cancer.

Study	*n*	Setting	Response rate, %	Median TTP, months	Median OS, months
Capecitabine monotherapy					
Phase III					
Hortobagyi et al.[1]	612	Anthracycline and taxane pretreated	29	4.4[a]	15.6
Thomas et al.[2]; Hortobagyi et al.[1]	377	Anthracycline and taxane pretreated	23	3.8[a]	11.1
Miller et al.[3]	230	Anthracycline and taxane pretreated	19	4.2	14.5
Cameron et al.[4]	201[b]	Anthracycline and taxane pretreated	14	4.3	15.3
Mavroudis et al.[5]	56	Anthracycline and taxane pretreated	24	5.0	14.6
Phase II					
Blum et al.[6]	162	Anthracycline and paclitaxel pretreated	20	3.1	12.6
Reichardt et al.[7]	136	Anthracycline and taxane pretreated	15	3.5	10.1
Fumoleau et al.[8]; Largillier et al.[9]	126	Anthracycline and taxane pretreated	28	5.9	15.9
Blum et al.[10]	74	Anthracycline and taxane pretreated	26	3.2	12.2
Range across all settings			14–29%	3.1–5.9	10.1–15.9
i.v. vinorelbine					
Phase III					
Martin et al.[11]	126	Anthracycline and taxane pretreated	26	4.0[a]	16.4
Jones et al.[12]	115	Anthracycline pretreated	16	2.8	8.0
Phase II					
Degardin et al.[13]	100	Anthracycline pretreated	16	NA	NA
Langkjer et al.[14]	60	Anthracycline pretreated	12	3.0	10.3
Toi et al.[15]	50	Anthracycline and taxane pretreated	20	3.4	NA
Range across all settings			12–26%	2.8–4.0	8.0–16.4
Oral vinorelbine					
Winer et al.[16]	131	Pretreated	11	NA	9.9
Amadori et al.[17]	72	NR	24	NR	NR
Range across all settings			11–24%	NA	9.9

TTP, time to progression; OS, overall survival; NA, not available; NR, not reported.
a Progression-free survival.
b HER2-positive MBC (immunohistochemistry 3+, or 2+ and fluorescence in situ hybridisation positive).

Table 2 – Summary of capecitabine (X) versus vinorelbine (V) comparative data.

Publication	*n*		RR		Median TTP, months		Median OS, months		1-year PFS	
	X	V	X	V	X	V	X	V	X	V
First-line setting										
Retrospective analysis[20]	53	20	NR	NR	NR	NR	15.1 (9.9–20.2)	7.2 (3.6–10.8)	NR	NR
Anthracycline- and taxane-pretreated MBC										
Randomised phase II[21]	23	24	9%	13%	2.8[a]	2.6[a]	9.3 (7.5–not reached)	11.0 (8.1–14.6)	NR	NR
Randomised phase III, X versus V[c] gemcitabine[5]	54	60[b]	24%	28%[b]	5.0	3.7[b]	14.6	12.5[b]	29%	17%[b]
Post-hoc analysis of post-study treatment in phase III trial[23]	28	50	NR	NR	NR	NR	21.0 (95% CI: 15.6–27.6) HR 0.500 ($p = 0.0046$)	13.5 (95% CI: 11.6–19.6) HR 1.014 (NS)	NR	NR
Retrospective analysis[24]	68	45	NR	NR	NR	NR	6.2 HR 0.46 ($p < 0.0001$)	3.4	NR	NR

RR, response rate; TTP, time to progression; OS, overall survival; PFS, progression-free survival; NR, not reported; MBC, metastatic breast cancer; CI, confidence interval; HR, hazard ratio; NS, not significant.
a Progression-free survival.
b Vinorelbine.
c Gemcitabine.

ment.[21] Reasons for slow accrual included the regulatory approval of capecitabine in this setting and patient preference for an oral versus an i.v. drug. Consequently, the planned expansion to a phase III trial was not undertaken. The limited qualitative data available from the phase II study suggest similar activity of the 2 agents but differing safety profiles, with more grade 3/4 toxicity occurring in patients receiving vinorelbine (predominantly neutropaenia, with or without fever).[21] Among the 24 patients receiving vinorelbine, 46% experienced grade 3/4 neutropaenia, and grade 3/4 neutropaenic fever, fatigue and abdominal pain each occurred in 13% of patients. In the capecitabine arm, no grade 3/4 adverse event occurred in more than 1 patient. As well as the premature discontinuation of the trial, failure to appropriately modify treatment doses in a considerable proportion of patients may have led to early withdrawal from study treatment. Thus findings from this study are difficult to interpret and do not provide evidence to assist in clinical decision making.

Further data on the relative efficacy of the 2 agents in anthracycline- and taxane-pretreated MBC come from a randomised, phase III trial comparing capecitabine monotherapy with vinorelbine in combination with gemcitabine,[5] an analysis of post-study treatment in the docetaxel arm of a randomised, phase III trial of docetaxel versus docetaxel plus capecitabine[22,23] and a retrospective analysis[24] (Table 2).

In the Greek randomised, phase III trial comparing capecitabine monotherapy with vinorelbine-gemcitabine combination therapy in anthracycline- and taxane-pretreated MBC, interim data suggest similar activity in the 2 treatment arms, with a trend towards better efficacy in the capecitabine monotherapy arm (median time to progression [TTP] 5.0 months versus 3.7 months with combined vinorelbine plus gemcitabine; 1-year progression-free survival [PFS] rates 29% versus 17%, respectively).[5] Capecitabine was associated with significantly more grade 3 hand-foot syndrome and significantly less grade 3/4 neutropaenia than vinorelbine plus gemcitabine. The trial is ongoing.

In a retrospective analysis of treatment after failure of an anthracycline and single-agent docetaxel in the phase III trial reported by O'Shaughnessy and colleagues,[22] capecitabine was associated with significantly longer OS than other chemotherapies (hazard ratio [HR] 0.500, representing a 50% lower risk of death, $p = 0.0046$; median 21.0 months versus 12.3 months, respectively), whereas there was no difference between vinorelbine and all other regimens (HR 1.014, $p = 0.94$).[23]

In the third dataset, retrospective analysis of capecitabine versus vinorelbine in anthracycline- and taxane-pretreated patients treated in 3 Canadian cancer centres demonstrated a significantly longer median OS in patients receiving capecitabine monotherapy (6.2 months) than vinorelbine monotherapy (3.4 months).[24] The longest median OS was seen in

Table 3 – Summary of grade 3/4 adverse events with capecitabine or vinorelbine monotherapy.[1,3–8,10–16,18,19,26–30]

	Capecitabine	Vinorelbine
Neutropaenia	1–14	44–74
Febrile neutropaenia	0–2	6–12
Anaemia	<1–4	5–14
Leucopaenia	0–7	46–75
Hand-foot syndrome	1–24	0
Diarrhoea	0–19	0–9
Constipation	0–1	2–14
Nausea/vomiting	2–12	0–13
Stomatitis	0–12	0–4
Dehydration	4–7	0
Fatigue/asthenia	2–10	3–17
Dyspnoea	0	0–6
Alopaecia	0	0–19
Elevated AST	0–4	4–6
Elevated ALT	2	2–6

AST, aspartate aminotransferase; ALT, alanine aminotransferase.

Table 4 – Summary of trials evaluating capecitabine (X) plus i.v. vinorelbine (V) in metastatic breast cancer (HER2 negative or unselected for HER2 status).

Study	Phase	*n*	Setting	Dose (X days 1–14, V days 1 and 8 unless otherwise stated)	Response rate	Median TTP, months	Median OS, months
Schott et al.[56]	I	25	Anthracycline and taxane pretreated	X 1500 mg b.i.d. (~862 mg/m2 b.i.d.) V 20–50 mg (~23 mg/m^2)	30%	NA	NA
Lorusso et al.[57]	I	18	2nd line, anthracycline and/or taxane pretreated	X 700–1125 mg/m^2 b.i.d. V 25 mg/m^2	38%	2.8	9.4
D'Aiuto et al.[58]	I	27	Anthracycline pretreated, 89% with taxane	X 1000–1250 mg/m^2 b.i.d. d1–14 q21d to 1250 mg/m^2 b.i.d. d1–10, q14d V 25–30 mg/m^2 weekly	48%	NA	NA
Sano et al.[59]	I	12	Anthracycline and taxane pretreated	X 825 mg/m^2 b.i.d. V 20–25 mg/m^2	25%	NA	NA
Hess et al.[60]	I	36	1st line (⩾65 years)	X 400–625 mg/m^2 b.i.d. V 20–25 mg/m^2	48–53%	4.5–5.3	NA
Favier et al.[61]	I	10	1st line	X 1000 mg/m^2 b.i.d. V 20–25 mg/m^2 days 1 and 15	NA	NA	NA
Domenech et al.[62]	Pilot	12	1st, 2nd or 3rd line	X 1000 mg b.i.d. (flat dose) V ~18 mg/m^2, days 1, 8, 15	58%	NA	NA
Nolè et al.[63]	Extended phase I	49[a]	90% 4th line or later	X 500–1250 mg/m^2 b.i.d. V 12.5–22.5 mg/m^2	37%	7.4	NA
Welt et al.[64]	I/II	33	1st line (30%) or 2nd line (70%), anthracycline and/or taxane pretreated	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	55%	8	19.2
Elghazaly et al.[65]	II	45	1st line	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	64%	9	NR
Ghosn et al.[66]	II	30	1st line	X 825 mg/m^2 b.i.d. V 25 mg/m^2	70%	10[a]	30.4
Ghosn et al.[67]	II	40	1st line	X 825 mg/m^2 b.i.d. V 25 mg/m^2 both for 4 cycles, followed by docetaxel 25 mg/m^2	55%	12.3 (NB sequential docetaxel)	35.8 (NB sequential docetaxel)
Ghosn et al.[68]	II	30	1st line	X 825 mg/m^2 b.i.d. V 25 mg/m^2 both for 8 cycles	70%	10	34
Köhler et al.[69]	II	30	HER2 negative, first line, ⩾60 years old	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	77%	NA	NA

Hess et al.[70]	II	70	1st line, ⩾65 years old	X 500 mg/m^2 b.i.d. (625 mg/m^2 b.i.d. patients without bone metastases) V 20 mg/m^2	43%[b]/57%[c]	4.3[b]/7.0[c]	NA
Iodice et al.[71]	II	53	1st line, ⩾65 years	X 1000–1250 mg/m^2 b.i.d. V 20–25 mg/m^2 Intrapatient dose escalation if well tolerated	62%	12.1[a]	21.3
Palumbo et al.[72]	II	32	1st line (91% prior anthracycline)	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	72%	9.1	NR
Range across phase II studies in first-line setting					43–77%	4.3–12.1	21.3–34
Stuart et al.[73]	II	58	Anthracycline pretreated	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	43%	NA	NA
Davis et al.[74]	II	22	Anthracycline pretreated, 64% taxane pretreated	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	33%	5.8	13.5
Orphanos et al.[75]	II	30	2nd line (anthracycline and/or taxane pretreated)	X 1000 mg/m^2 b.i.d. V 20 mg/m^2	50%	NA	NA
Estevez et al.[76]	II	31	Anthracycline and taxane pretreated	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	49%	7.6	27.2
Lorusso et al.[77]	II	38	Anthracycline and/or taxane pretreated	X 1000 mg/m^2 b.i.d. V 25 mg/m^2	37%	6.8	11.3
Xu B et al.[78]	II	77	2nd line	X 950 mg/m^2 b.i.d. V 25 mg/m^2	47%	6	NA
Ahn et al.[79]	II	44	Anthracycline and taxane pretreated	X 1250 mg/m^2 b.i.d. V 25 mg/m^2	50%	5.3[a]	17
Range across phase II studies in pretreated setting MBC					33–50%	5.3[a]–7.6	11.3–27.2

TTP, time to progression; OS, overall survival; NA, not available; NR, not reached.
*Progression-free survival (TTP not reported).
a 31% of patients had HER2 overexpression.

patients receiving both agents sequentially in either order (12.8 months).

Capecitabine and vinorelbine have been compared in a pharmacoeconomic analysis, a crucial consideration in modern healthcare. The component chemotherapy-related costs to total direct medical expenditures were evaluated in MBC patients receiving capecitabine or vinorelbine monotherapy in the Unites States of America.[25] Mean monthly total direct expenditure was significantly lower in patients receiving capecitabine than in matched patients receiving vinorelbine ($7032 versus $9460, respectively; $p < 0.0001$). The difference was driven by significantly lower costs of managing complications ($p < 0.0001$) and chemotherapy administration ($p < 0.0001$) in the capecitabine group. Patients receiving capecitabine were at significantly lower risk of myelosuppression (HR 0.27, $p < 0.0001$), constitutional symptoms (HR 0.67, $p = 0.01$) and gastrointestinal events requiring prescription medications or deemed clinically significant (HR 0.27, $p < 0.0001$) compared with vinorelbine users. Significantly lower chemotherapy administration costs with capecitabine ($42 versus $410 with vinorelbine; $p < 0.0001$) resulted in significantly lower monthly costs ($1028 versus $1408, respectively; $p < 0.0001$).

2. Combination of capecitabine and vinorelbine

An alternative approach has been to combine the 2 agents. Capecitabine has been combined with a wide range of chemotherapeutic and biologic agents. It is an attractive combination partner offering high single-agent activity and a non-overlapping toxicity profile, with minimal myelosuppression and no alopaecia. The most frequent side-effects are palmar plantar erythrodysaesthesia (hand-foot syndrome) and gastrointestinal effects, most frequently diarrhoea (Table 3).

Vinorelbine is most commonly used as monotherapy, although several trials suggest that vinorelbine combined with i.v. 5-fluorouracil (5-FU) is active.[31–39] Vinorelbine has also been tested in clinical trials in combination with doxorubicin (pegylated or conventional)[40–46] or epirubicin[47–50] and as a component of triplet combinations with epirubicin, taxane, gemcitabine and/or 5-FU.[51–54] The most common grade 3/4 adverse effect of vinorelbine is myelosuppression (Table 3).

The rationale for combining capecitabine and vinorelbine is based on their non-overlapping safety profiles and preclinical synergy. Like many chemotherapeutic agents, vinorelbine upregulates thymidine phosphorylase (TP),[55] which has a crucial role in the 3-step conversion of capecitabine to 5-FU preferentially at the tumour site.

3. HER2-negative disease

3.1. *Capecitabine plus i.v. vinorelbine*

Numerous phase I and II studies of capecitabine plus i.v. vinorelbine in patients with HER2-negative MBC or who were unselected for HER2 status have been conducted and are summarised in Table 4. In phase I dose-escalation studies, a 3-weekly regimen of capecitabine 1000 mg/m^2 twice daily (b.i.d.), days 1–14, plus i.v. vinorelbine 25 mg/m^2 on days 1 and 8 was frequently identified as the most appropriate schedule. Across all of these early studies, the most frequent dose-limiting toxicities were haematological (grade 3/4 neutropaenia, febrile neutropaenia).

In subsequent single-arm, phase II studies, RRs of 33–50% were reported in pretreated MBC. In this setting, median TTP was approximately 5–8 months and median OS was 11–27 months in the 4 trials for which data are available.[74,76,77,79] In the first-line setting, RRs of up to 77% have been reported. Median OS ranges from 21 to 34 months in these small, single-arm studies including between 30 and 53 patients.[66,68,71]

The toxicity of the combination of vinorelbine and capecitabine is consistent with the known side-effects of each agent, most notably neutropaenia, which is characteristic of vinorelbine (Table 3, Fig. 1). Studies conducted specifically in elderly patients have shown good efficacy and tolerability of the combination.[69–71] The only grade 3/4 adverse events in >10% of patients were neutropaenia in the Italian (30%) and Swiss (20%) studies and pain in the German study (15%). Quality of life data collected in the study by the SAKK (Switzerland) in patients $\geqslant$65 years revealed no substantial change in physical wellbeing versus baseline across all timepoints.[70]

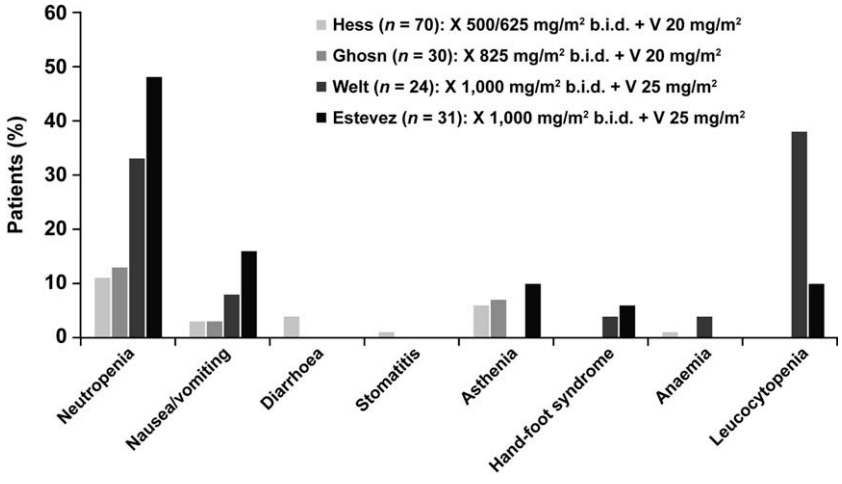

Fig. 1 – Summary of tolerability of capecitabine plus i.v. vinorelbine combination therapy: published phase II studies, grade 3/4 adverse events by patient.[64,66,70,76]

3.2. *Capecitabine plus oral vinorelbine*

More recently, an oral formulation of vinorelbine has become available. In pharmacokinetic studies, equivalent bioavailability was shown with an oral versus intravenous dose.[80] Although there are very few clinical trials of oral vinorelbine, no mature overall survival data and no randomised trials versus other chemotherapeutic agents, oral vinorelbine is reported to offer similar efficacy to i.v. vinorelbine, with improved convenience and tolerability.[81] This provides the opportunity to develop an all-oral combination regimen, which may be preferred by many patients.[82–85]

In 2 phase I dose-escalation studies, a regimen of capecitabine 1000 mg/m^2 b.i.d. for 14 days every 3 weeks combined with oral vinorelbine 60 mg/m^2, days 1 and 8, was identified for further evaluation.[86,87] In single-arm, phase II studies, this combination (most commonly utilising capecitabine at 1000 mg/m^2 b.i.d. days 1–14 and vinorelbine 60–80 mg, days 1 and 8 every 3 weeks) has demonstrated RRs of 26–61%, as shown in Table 5. These RRs compare favourably with RRs for either therapy alone. However, in pretreated disease, the apparent improvement in RR does not appear to translate to improved outcomes. For example, in anthracycline- and taxane-pretreated patients, Lorusso and colleagues reported median OS of 10 months,[77,95] similar to the lower end of the range reported for capecitabine monotherapy in this setting (10.1–15.9 months) in large phase II and III trials.[1–3,5–10] Median OS was 17.5 months in a Czech trial in anthracycline-pretreated MBC but data are relatively immature (median follow-up of 10 months).[93]

In the first-line setting, an all-oral regimen of capecitabine and vinorelbine demonstrated identical median PFS of 8.4 months in 2 relatively small ($n = 52$ and 54) single-arm studies.[90,91] Median OS was 29.2 months (95% CI: 18.2–40.1) in the multinational study of 54 patients with HER2-negative MBC reported by Tubiana-Mathieu and colleagues after a

Table 5 – Summary of trials evaluating an all-oral regimen of capecitabine (X) plus vinorelbine (V) in metastatic breast cancer (HER2 negative or unselected for HER2 status).

Study	Phase	N	Setting	Dose (X days 1–14, V days 1 and 8 unless otherwise stated)	Response rate	Median TTP, months	Median OS, months
Kellokumpu-Lehtinen et al.[86]	I	21	Anthracycline and/or taxane pretreated	X 1000 mg/m^2 b.i.d., days 2–7 and 9–14 V 40–80 mg/m^2	11%	NA	NA
Nolè et al.[87]	I	44	1st or 2nd line	X 825–1250 mg/m^2 b.i.d. V 60–80 mg/m^2	41%	7.7[a]	NR
Anton et al.[88]	I	18	Any line 72% 1st line	X 825–1000 mg/m^2 b.i.d. V 60–80 mg/m^2	28%	NR	NR
Gligorov et al.[89]	Pilot	16	HER2 negative, any line (81% anthracycline pretreated)	X 1000 mg/m^2 b.i.d. V 60 mg/m^2	25%	4.5	NA
Tubiana-Mathieu et al.[90]	II	54	HER2 negative, 1st line	X 1000 mg/m^2 b.i.d. V 60 mg/m^2 escalating to 80 mg/m^2, cycle 2	51%	8.4[a]	29.2
Nolè et al.[91]	II	52	1st line	X 1000 mg/m^2 b.i.d. V 60 mg/m^2, days 1, 8 and 15	44%	8.4[a]	25.8
Delcambre et al.[92]	I/II	35[b]/46[c]	1st or 2nd line	X 800–1250 mg/m^2 b.i.d. V 40–80 mg/m^2	51%[a]/61%[c]	6.8[a]	NA
Finek et al.[93]	II	115	1st or 2nd line	X 1000 mg/m^2 b.i.d. V 60 mg/m^2	56%	10.5[a]	17.5
Gil-Delgado et al.[94]	II	29	MBC, any line	X 1000 mg/m^2 b.i.d. V 60 mg/m^2	26%	6[a]	48
Lorusso et al.[77,9577,95]	II	38	Anthracycline and taxane pretreated	X 1000 mg/m^2 b.i.d., days 2–7 and 9–16 V 60 mg/m^2	39%	7	10
Range across phase II studies, all settings					26–61%	6–10.5[a]	10–48

TTP, time to progression; OS, overall survival; NA, not available; NR, not reported.
a Progression-free survival (TTP not reported).
b Phase I.
c Phase II.

median follow-up of 41 months[90] and 25.8 months (95% CI: 21.6–33.6) in the Italian study reported by Nolé and colleagues after a median follow-up of 30.3 months.[91] No randomised trials of this all-oral combination have been reported.

Grade 3/4 neutropaenia was reported in 49% of patients in the multinational study.[90] However, grade 3 hand-foot syndrome and grade 3/4 diarrhoea appear to be less problematic, each occurring in only 4% of patients. This may reflect the better tolerability of capecitabine 1000 mg/m^2 b.i.d., reduced to 750 mg/m^2 b.i.d. in patients aged $\geqslant$65 years (comprising 41% of the study population). The median number of cycles delivered in Tubiana-Mathieu and colleagues' single-arm phase II study was 7 (range 1–58). The possibility of continuing therapy for prolonged periods in patients with controlled disease is a noteworthy benefit over anthracycline- or taxane-containing combination regimens, with which cumulative toxicity prevents long-term administration.

4. HER2-positive disease

Trastuzumab is the standard of care for patients with HER2-positive MBC. Trastuzumab is frequently combined with a taxane, and recent data suggest that efficacy can be improved further with the addition of capecitabine to a trastuzumab-taxane combination in the first-line setting.[96] However, for patients in whom taxanes are not an appropriate treatment, trastuzumab has often been partnered with i.v. vinorelbine.[97–100] More recently, as in HER2-negative disease, oral vinorelbine has been evaluated as an alternative to the i.v. formulation. The RR in 17 patients with HER2-positive disease treated in a pilot study[101] is within the range reported for the combination of i.v. vinorelbine plus trastuzumab in this setting, and is supported by results of an observational study of oral vinorelbine plus trastuzumab.[102] In the only randomised trial of trastuzumab plus (i.v.) vinorelbine (TRAVIOTA), the trastuzumab-vinorelbine combination demonstrated similar efficacy to trastuzumab plus weekly taxane (paclitaxel or docetaxel) but the trial was closed prematurely after accrual of 81 patients due to slow recruitment.[103]

Alternatively, trastuzumab can be combined with capecitabine, as demonstrated in the recently published randomised, phase III trial by the German Breast Group.[104] GBG26, conducted in patients whose disease had progressed on previous chemotherapy- and trastuzumab-containing therapy, demonstrated significantly improved TTP among patients receiving the combination of trastuzumab plus capecitabine versus those receiving capecitabine alone. The HR for TTP, the primary end-point, was 0.69 in favour of the trastuzumab-capecitabine combination ($p = 0.034$). Median TTP was 8.2 months (95% CI: 7.3–11.2) with the combination versus 5.6 months (95% CI: 4.2–6.3) in the capecitabine monotherapy arm. There was a trend towards improved OS in the trastuzumab–capecitabine combination arm (HR 0.75; median 25.5 versus 20.3 months), although this did not reach statistical significance at the time of the final analysis. These findings are consistent with efficacy observed in 5 single-arm, prospective, phase II studies evaluating the trastuzumab-capecitabine combination.[105–109] Thus trastuzumab-capecitabine appears to be an active and well-tolerated regimen for patients in whom trastuzumab- and taxane-containing therapy is not an option.

Trastuzumab in combination with capecitabine and docetaxel (HXT) has been evaluated in a second large, randomised trial, CHAT, conducted in the first-line setting. Patients with HER2-positive MBC were randomised to either trastuzumab plus docetaxel or HXT.[96] The addition of capecitabine to trastuzumab plus docetaxel resulted in significantly superior TTP (HR 0.704, $p = 0.029$) and PFS (HR 0.725, $p = 0.0402$). Median TTP and PFS durations were both increased by 5 months with the addition of capecitabine. One- and 2-year survival rates also favoured the capecitabine-containing regimen, although OS data are not yet mature.

Although the HXT combination has shown considerable efficacy, not all patients are candidates for taxane therapy (e.g. those with rapid relapse after adjuvant taxane-containing therapy, unacceptable taxane-associated toxicity in the adjuvant setting, severe liver dysfunction or patient refusal of a therapy causing hair loss). Nevertheless, some of these patients may benefit from first-line combination chemotherapy and in these cases, a triple combination of trastuzumab, capecitabine and vinorelbine (HXN) is a validated option. Interim results from a multinational, single-arm trial evaluating this combination (with vinorelbine administered orally) demonstrated an overall RR of 77%,[110] similar to the RR seen with HXT in the CHAT trial,[96] although the complete response rate was slightly lower (18% versus 23% with HXT). OS data for HXN are not yet mature, with 66% of patients still alive after median follow-up of 28.5 months. Median PFS was 12.8 months.

Capecitabine has also been evaluated in combination with the dual tyrosine kinase inhibitor lapatinib in HER2-positive disease that has progressed after previous anthracycline-, taxane- and trastuzumab-containing therapy.[4,111] A randomised, phase III trial demonstrated that the addition of lapatinib to capecitabine significantly improved TTP (the primary end-point) and RR. At the most recent analysis, the HR for TTP was 0.57 ($p < 0.001$) and median TTP was 6.2 months with the combination of lapatinib and capecitabine versus 4.3 months with capecitabine alone. As in GBG26, there was no difference in OS between the treatment arms.

5. Discussion

The available data from 4 retrospective analyses comparing capecitabine and vinorelbine suggest that capecitabine is associated with better patient outcome than i.v. vinorelbine. However, prospective, randomised data are very limited and no comparison with oral vinorelbine has been undertaken. Treatment decisions for individuals should take into account the available trial results together with other considerations, such as prior therapy, comorbidities, organ function, tolerability and patient preference.

In the subset of patients requiring combination chemotherapy, but who are not suitable for a taxane-based regimen (e.g. prior exposure to taxane, underlying peripheral neuropathy or patient choice based on potential adverse effects), a combination of vinorelbine and capecitabine may be considered, although there are no randomised, phase III data to sup-

port this strategy. In particular, the combination has not been compared with sequential administration of capecitabine and vinorelbine monotherapies. In the absence of randomised data, cross-trial comparison provides the only signal for relative efficacy of the combination but must be viewed with caution. Combination therapy with capecitabine and i.v. vinorelbine may improve efficacy over either drug alone but appears to increase adverse events, particularly myelosuppression. The median TTP in phase II studies in pretreated disease is 5–7 months, compared with 3–5 months with capecitabine[2,3,5–8,10] and 3–4 months with vinorelbine.[11,15] There are no robust data allowing a comparison of OS rates. A randomised, phase III trial by the Greek co-operative group, HECOG, is comparing capecitabine plus i.v. vinorelbine versus capecitabine alone in taxane-pretreated, HER2-negative MBC and may provide clarification.

In most studies of capecitabine and i.v. vinorelbine, the capecitabine dose was 1000 or 1250 mg/m^2 b.i.d. However, a regimen of capecitabine 825 mg/m^2 b.i.d. in combination with vinorelbine 25 mg/m^2 showed high activity in phase II studies,[66,68] suggesting that a lower dose of capecitabine is effective. The activity was similar to that when capecitabine 825 mg/m^2 b.i.d. is combined with taxane.[112] Thus the capecitabine–vinorelbine combination regimen appears to be a valid, non-taxane-containing regimen for patients who require combination therapy with the objective of increasing RR but who are not candidates for taxane therapy and/or wish to avoid specific taxane-associated toxicities, in particular alopaecia and neuropathy.

In contrast to the findings when capecitabine and i.v. vinorelbine are combined, the efficacy of an all-oral combination of capecitabine and vinorelbine appears to offer no clear benefit over capecitabine monotherapy in pretreated HER2-negative disease:[95] cross-trial comparison hints at shorter TTP and OS with the combination in this setting, despite a slightly higher RR. There are no published phase II/III data of oral vinorelbine as monotherapy in this setting. Thus capecitabine monotherapy appears to be a preferable approach and is supported by consistent activity in large phase II and III trials.

In first-line treatment of MBC, encouraging RR, PFS and OS data have been reported with the all-oral combination but again, no studies have compared the combination with sequential monotherapy. Addition of capecitabine to oral vinorelbine appears to double median PFS, based on cross-trial comparison, whereas the benefit of adding vinorelbine to capecitabine is less convincing.

In HER2-positive MBC, median OS is similar when trastuzumab is combined with either capecitabine or vinorelbine, and therefore other considerations, such as tolerability and patient preference should be taken into account when selecting therapy. Randomised data are available for lapatinib plus capecitabine but not the combination of vinorelbine and capecitabine. For patients requiring more intensive therapy, randomised data show that HXT provides significantly longer TPP and PFS than trastuzumab–docetaxel alone. In patients with MBC who relapse following trastuzumab- and taxane-containing adjuvant therapy, the triple combination of HXN shows promise, although OS data are immature.

Based on a comprehensive review of available data, it appears that capecitabine is a more effective monotherapy than vinorelbine. In the subset of patients in whom combination chemotherapy is required, addition of i.v. vinorelbine to capecitabine may improve outcomes, although a wide range of other combination partners should be considered, including taxane-containing regimens that have proven high efficacy. In pretreated disease, the addition of oral vinorelbine to capecitabine adds haematological toxicity without any apparent improvement in activity. The need for more frequent haematological monitoring when oral vinorelbine is combined with capecitabine may reduce the convenience of an all-oral regimen. To date there is no clear population for whom this combination can be recommended over capecitabine monotherapy, although recently presented survival data from a single-arm, phase II study in HER2-negative disease are encouraging.

6. Conclusion

For the majority of patients, capecitabine monotherapy appears to be the more effective agent for patients with prior taxane exposure or who are unsuitable for taxane therapy and has the most supportive clinical trial dataset. Combination regimens of capecitabine and vinorelbine show promise but need further evaluation against effective sequential, monotherapy strategies before the combination can be recommended for routine use.

Conflict of interest statement

Dr. Chan is a medical advisor on the national advisory board for Roche and has received honoraria for speaking at educational meetings for Roche and Pierre Fabre. Dr. Verrill has received research funding and honoraria for lectures and consultancy from Pierre Fabre. He has received research funding, support for attending conferences and honoraria for lectures from Roche, for whom he acts as a consultant.

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