Overview

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Title: A Randomized Feasibility Study of Docetaxel Versus Vinorelbine in Advanced Breast Cancer

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Author Summary: Abstract and Brief Discussion

Background

Docetaxel and vinorelbine have demonstrated efficacy in the treatment of metastatic breast cancer (MBC). This prospective feasibility study compared the efficacy of these two treatments in MBC.

Methods

Patients with MBC progressing following anthracycline treatment were randomly assigned to either docetaxel (100mg/m² day 1 q3W) or vinorelbine (25mg/m² day 1 q2W). Patients were eligible to cross over at progression. Objective response rates (ORR), time to progression (TTP) and overall survival (OS) were measured.

Results

37 patients were randomised. 2 patients were excluded due to protocol violations. Of 35 remaining patients 17 received docetaxel and 18 received vinorelbine per protocol. ORR was 12.5% and 6.0% respectively for docetaxel and vinorelbine. The median time to progression was 10.4 weeks (range 6-14 weeks) in docetaxel arm and 7.6 weeks (range 4-11 weeks) in vinorelbine arm ($p = .82$). The clinical benefit rate (defined as complete response, partial response plus stable disease) was 44% in the docetaxel arm and 12% in the vinorelbine arm. Based on intent to treat the median OS in the docetaxel arm was 34 weeks (95% CI, 20.7-48) and 21.2 weeks (95% CI, 17-25.4) in vinorelbine arm ($p = .388$). 16 patients crossed over, 5 from docetaxel to vinorelbine and 11 from vinorelbine to docetaxel. At cross over the ORR was 0% and 18% on cross over to vinorelbine and docetaxel respectively with a median TTP of 17.3 weeks (95% CI, 16.3-18.1) and 18.7 weeks (95% CI, 13.9-23.4) for those receiving vinorelbine and docetaxel at cross over respectively. Vinorelbine however was much better tolerated with fewer grade 3-4 toxicity events ($n = 4$) than docetaxel ($n = 27$).

Discussion

While docetaxel resulted in a longer TTP and OS in this study it did not reach statistical significance. TTP duration for those patients who crossed over was similar, but overwhelmingly vinorelbine had fewer significant grade 3-4 toxicities than docetaxel. Only two previous randomized studies have compared the efficacy of single agent docetaxel and vinorelbine following prior anthracycline exposure, one in an unselected population [16], and the other, HERNATA, in HER2 positive disease with trastuzumab used in both arms [17]. The patients randomized in this study were relatively heavily pretreated with the majority having received 2-3 lines of prior treatment for their metastatic disease. The lower response rates with vinorelbine as compared to docetaxel in this study concur with results reported in other studies [16]. However, the numbers in both this study and the other unselected study [16] are small and need to be interpreted with caution. With regard to toxicity, in the present study, grade 3-4 hematological adverse events and infection were tenfold greater with docetaxel as compared with vinorelbine, consistent with results in HERNATA [17]. While others have reported a significantly higher number of overall grade 3-4 toxicities with vinorelbine [16], the fact that, as in HERNATA, discontinuations due to toxicities in that study [16] were significantly greater with docetaxel as compared to vinorelbine suggests either the toxicity data collected did not reflect the true toxicities on treatment or that docetaxel toxicities were in some way more severe or protracted leading to more numerous discontinuations [16]. Larger randomized studies are needed to determine (1) the efficacy of docetaxel versus vinorelbine in anthracycline pretreated disease and (2) the efficacy of vinorelbine after prior taxane exposure, and particularly how it may compares both with regard to efficacy and tolerability with other possible regimens that may utilized such as carboplatin-gemcitabine [20] or eribulin [21]. The longer as well as comparable TTP at cross over for both agents compared to that upfront suggests there may be enrichment at cross over of a group of patients who are not only fit for further treatment but are more likely to derive continued benefit from additional treatment.

Trial Information

Disease:	Breast cancer
Stage of disease/treatment:	Metastatic / Advanced
Prior Therapy:	1 prior regimen
Type of study – 1:	Exploratory
Type of study – 2:	Randomized
Secondary Endpoint:	Overall Response Rate
Secondary Endpoint:	Time to Progression
Additional Details of Endpoints or Study Design:	Randomized cross over study comparing vinorelbine vs docetaxel.

Investigator's Assessment of Activity: Active

Drug Information

Drug 1:

Generic/Working name:	Vinorelbine
Trade name:	Navelbine
Drug type:	Other
Drug class:	Tubulin / Microtubules targeting agent
Dose:	25 milligrams (mg) per
Route:	IV
Schedule of Administration:	2 weekly

Drug 2:

Generic/Working name:	Docetaxel
Trade name:	Taxotere
Drug type:	Other
Drug class:	Tubulin / Microtubules targeting agent
Dose:	100 milligrams (mg) per
Route:	IV
Schedule of Administration:	3 weekly

Patient Characteristics

Number of patients, male:	0
Number of patients, female:	37
Stage:	IV
Age:	Median (range): 45 (33-67)
Number of prior systemic therapies:	Median (range): 2 (1-3)
Performance Status: ECOG:	Not Collected
Other:	PS < 2
Cancer Types or Histologic Subtypes: Not Given	

Experimental Arm: Total Patient Population

Number of patients screened:	0
Number of patients enrolled:	18
Number of patients evaluable for toxicity:	18
Number of patients evaluated for efficacy:	16
Evaluation method:	Other
Response assessment CR:	0%
Response assessment PR:	2%
Response assessment SD:	5%
Response assessment PD:	9%
Response assessment other:	0%
(Median) duration assessments PFS:	0%
(Median) duration assessments TTP:	10.4 weeks, CI: 6.3-14.4
(Median) duration assessments OS:	34 weeks, CI: 20.7-48
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	N/A

Control Arm: Total Patient Population

Number of patients screened:	0
Number of patients enrolled:	19
Number of patients evaluable for toxicity:	18
Number of patients evaluated for efficacy:	18
Evaluation method:	Other
Response assessment CR:	0%
Response assessment PR:	1%
Response assessment SD:	1%
Response assessment PD:	16%
Response assessment other:	0%
(Median) duration assessments PFS:	
(Median) duration assessments TTP:	7.6 weeks, CI: 4-11
(Median) duration assessments OS:	21.2 weeks, CI: 17-25.4
(Median) duration assessments response duration:	N/A
(Median) duration assessments duration of treatment:	N/A

Adverse Events

Name	*NC/NA	1	2	3	4	5	All Grades
*No Change from Baseline/No Adverse Event							
Neutrophils/granulocytes (ANC/AGC)	0%	34%	17%	34%	13%	0%	100%
Infection (documented clinically or microbiologically) with Grade 3 or 4 neutrophils (ANC <1.0 x 10e9/L)	0%	10%	20%	40%	30%	0%	100%
Fatigue (asthenia, lethargy, malaise)	0%	22%	22%	33%	22%	0%	100%
Hemoglobin	0%	55%	35%	10%	0%	0%	100%
Platelets	0%	50%	33%	16%	0%	0%	100%

Adverse Events Legend: Adverse events with docetaxel.

Serious Adverse Events

Name	Grade	Attribution
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Assessment, Analysis, and Discussion

Completion:	Study completed
Completed Study Assessment:	Active
Pharmacokinetics/Pharmacodynamics:	Not Collected
Investigator's Analysis:	Active but results overtaken by other developments

Discussion

This study compared the efficacy and toxicity of single agent vinorelbine administered every two weeks with single agent docetaxel administered every three weeks in metastatic breast cancer previously treatment with an anthracycline; additionally efficacy of cross over to the alternate treatment on disease progression was also explored. The patients randomized into this study were relatively heavily pretreated, with the majority having received 2-3 lines of prior treatment for their metastatic disease. With regard to efficacy the ORR were higher at initial treatment with docetaxel as compared to vinorelbine, 12% versus 6% respectively, with a clinical benefit rate of 43% versus 10% respectively. The higher response rate seen with single agent docetaxel as compared to single agent vinorelbine when administered as the first treatment in this trial is in keeping with the ORR published in other studies [16]. The ORR with docetaxel as initial treatment within this study is lower than that reported in previous studies, where ORR of 30-69% have been reported with docetaxel in anthracycline pre-treated patients [3-5, 16]. Similarly, the ORR to vinorelbine is lower than that previously reported, with ORR of 10-40% documented [9-11, 12, 14, 15]. It should be noted that the majority of these studies were non-randomised and many differed from this study in terms of the vinorelbine regimen used and the patient population selected. In those that were randomised the ORR to vinorelbine was 16-18% [8, 16].

The reasons for the differences seen between this study and the others previously reported may be due to the small numbers in the present study and differences in the patient population. It should be noted the patients in the current study

were more heavily pre-treated with over 80% having been exposed to 2 or more lines of palliative treatment as compared to 40-48% in the only other randomized comparison [16]. Unlike docetaxel, the schedule of vinorelbine used in this study is different from many of the others, however this schedule; 25 mg/m² every 2 weeks has previously been reported to be efficacious [12].

In the present study docetaxel was associated with greater grade 3 and 4 toxicities than vinorelbine. It is difficult to compare directly with other studies since the schedules are different, however there are important implications for treatment in the metastatic setting. Grade 3-4 hematological and infection toxicities with vinorelbine were very uncommon (n=2), whereas docetaxel was associated with a tenfold greater incidence of serious infective and hematological toxicities (n=20) (Table 5). Our results are consistent with those seen in HERNATA in which grade 3/4 toxicities occurred significantly more frequent with docetaxel, including febrile neutropenia, leucopenia, infection, fever, sensory neuropathy, nail changes, and edema. Others have reported a significantly higher number of overall grade 3 and 4 toxicities with vinorelbine both as initial treatment and following cross over, however the scheduling in that study was different to that reported here [16]. However, as in HERNATA, discontinuations due to toxicities were significantly greater with docetaxel as compared to vinorelbine [17]. The data presented here which show a total of 27 grade 3-4 toxicity events with docetaxel amongst all randomized patients, explain the high rate of discontinuation or interruption of treatment with this agent. Dose modifications to 55-75 mg/m² were mandated in a number of studies if due to toxicities [3, 4, 6, 17]. It is not unreasonable in the metastatic setting to consider commencing patients, at a starting dose of 75 mg/m², as the goal is palliation of symptoms and quality of life. Furthermore the results presented here confirm the tolerability and safety of vinorelbine administered every two weeks in heavily pre-treated patients with only 4 grade 3/4 events across all categories of toxicity amongst all randomized patients.

This study was a feasibility study with a small sample size which is a limitation, however the data with regard to the greater efficacy and toxicity of docetaxel are in keeping with other studies.

In conclusion, single-agent docetaxel (100 mg/m²; q3w) results in a higher ORR and a numerically longer PFS compared to single agent IV vinorelbine (25 mg/m²; q2w), however it is associated with more hematological toxicities. In addition, the efficacy of docetaxel post vinorelbine is greater than that for vinorelbine following docetaxel. Our results, would tend to fit in with other data showing that docetaxel is on balance a more efficacious agent compared to vinorelbine in patients with prior anthracycline exposure but is associated with greater toxicities. As always clinician will need to balance the possible benefits in individual cases with the toxicities that may more readily be encountered with one agent as compared to another.

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Figures and Tables

[consort_diagram.pptx](#) — Consort Diagram of Patients Randomized to Receive Study Drugs.

A randomised feasibility study of docetaxel versus vinorelbine in advanced breast cancer.

Response	Docetaxel, n (%)	Vinorelbine, n (%)
	17	18
CR+PR	2 (12.5)	1 (6.0)
SD	5 (31.25)	1 (6.0)
PD	9 (56.25)	16 (88)
Not Assessable	1	

Table 2: Summary of response data following randomisation to docetaxel and vinorelbine.
CR: Complete response; PR: Partial response; SD: Stable Disease; PD: Progressive Disease

Response	Docetaxel to Vinorelbine, n (%)	Vinorelbine to Docetaxel, n (%)
	5	11
CR+PR	0	2 (18)
SD	2 (40)	7 (64)
PD	3 (60)	2 (18)

Table 3: Summary of response data following cross over from docetaxel to vinorelbine or vinorelbine to docetaxel.
CR: Complete Response; PR: Partial Response; SD: Stable Disease; PD: Progressive Disease.

	Vinorelbine	Docetaxel
No. of Cycles pre Cross over	2-12	1-6
Median	4	5
No. of Cycles post Cross over	1-6	1-6
Median	5	5

Table 4: Summary of total number and median number of chemotherapy cycles given of vinorelbine and docetaxel pre and post cross over (for patients who received study drugs according to protocol).

T12-161CTR_R2_Palmieri_Revised_Patient_Characteristics.docx — Table 1 Patient characteristics according to initial treatment arm

	Docetaxel	Vinorelbine
Total Number of Patients	18	19
Age Range (Median)	33 – 67 (45)	30 -71 (52)
Hormone Receptor Status		
ER +ve/PgR +ve/unknown	4	3
ER +ve/PgR-ve	7	6
ER-ve/PgR+ve/unknown	1	2
ER-ve/PgR-ve	6	6
ER & PgR Unknown	0	2
Metastatic Disease		
Skin		
Local	6	10
Lymphadenopathy	2	6
Visceral		
Lung	8	10
Liver	7	4
Peritoneal	1	0
CNS	0	1
Bone	10	8
Previous Chemotherapy		
Neoadjuvant/Adjuvant only	8	10
Advanced Disease only	3	0
Neoadjuvant/Adjuvant and Advanced Disease	7	9
Previous Endocrine Therapy		
Adjuvant	12	12
Advanced Disease	7	2
Number of Previous Lines of Treatment		
1	3	3
2	7	9
3	8	7
Previous anthracycline exposure	18	19

Event	Drug	Grade 1-2	Grade 3-4	Total
Neutropenia	Docetaxel	12	11	23
	Vinorelbine	11	1	12
Anaemia	Docetaxel	18	1	19
	Vinorelbine	14	0	14
Thrombocytopenia	Docetaxel	5	1	6
	Vinorelbine	1	1	2
Fatigue	Docetaxel	4	5	9
	Vinorelbine	4	2	6
Transaminase	Docetaxel	11	2	13
	Vinorelbine	8	0	8
Infections	Docetaxel	3	7	10
	Vinorelbine	3	0	3

Table 5. Chemotherapy related toxicity as graded by Common Toxicity Criteria.

Figure 1. Per protocol analysis showing for time to progression (TTP) following randomisation to docetaxel or vinorelbine.

TTP (weeks) vinorelbine docetaxel
Median (95%CI) 7.6(4-11) 10.4(6.3-14.4)

Log Rank (Mantel-Cox) Chi-square 3.016, DF 1, Sig 0.082.

Figure 2. Per protocol analysis of time to progression or death following crossover from initial randomised study drug.

TTP (weeks) Vinorelbine to Docetaxel Docetaxel to Vinorelbine
Median (95%CI) 18.7(13.9-23.4) 17.3(16.3-18.1)

Log Rank (Mantel-Cox) Chi-square 0.503, DF 1, Sig 0.478.

Figure 3. Overall survival for all patients randomised on intent to treat analysis.

TTP (weeks) Vinorelbine Docetaxel
Median (95%CI) 21.2 (17-25.4) 34.4 (20.7-48)

Log Rank (Mantel-Cox) Chi-square 0.747, DF 1, Sig 0.388.

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