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ORIGINAL ARTICLE

Sequential vinorelbine–capecitabine followed by docetaxel in advanced breast cancer: long-term results of a pilot phase II trial

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Abstract
Purpose To evaluate the response rate of the combination of capecitabine (C) and vinorelbine (V) followed by Docetaxel (D) in the 1st line treatment of advanced and metastatic breast cancer patients.
Patients and methods Patients with measurable disease and no prior chemotherapy in advanced disease were eligible. Pts received V 25 mg/m^2 on day 1 and 8 in combination with C 825 mg/m^2 twice a day from day 1 to 14 every 3 weeks for four cycles followed by 12 consecutive weeks of D 25 mg/m^2/w.
Results Between March 2002 and November 2003, 40 patients were enrolled. Median age was 57 years. Of patients, 77.5% of pts had visceral involvement and 32.5% had more than two metastatic sites. In the adjuvant setting, 62.5% received anthracycline and 10% Taxanes. In the intent-to-treat population, an overall objective response was observed in 25 patients (62.5, 95% CI, 45.8–77.27) and stable disease in 5 (12.5%). Median time till progression (TTP) was 12.3 months (range 1.5–48; 95% CI, 10.05–14.54). The median survival was 35.7 months (range 2–47). Reported grade 3–4 toxicities under Navcap were neutropenia (4 pts), anemia (1 pt), thrombopenia (1 pt) and febrile neutropenia (3 pts). Reported grade 3–4 toxicities under weekly Docetaxel were neutropenia (1 pt), thrombopenia (2 pts), leucopenia (1 pt) and anemia (1 pt).
Conclusion The sequential use of Navcap followed by weekly Docetaxel demonstrated an interesting efficacy with a prolonged TTP and OS and warrants further evaluation.

Keywords Navcap · Vinorelbine · Capecitabine · Docetaxel · Metastatic breast cancer · First-line · Chemotherapy

Rational

Despite adjuvant chemotherapy, approximately 40–50% of patients will develop recurrent and/or metastatic breast cancer (MBC). The average survival time from the diagnosis of MBC is 18–30 months [1]. Systemic chemotherapy offers palliation to patients who failed hormonal therapy or were hormonally insensitive [2].

Vinorelbine, a third generation of vinca alkaloid has demonstrated its effectiveness as an option for the treatment of MBC patients. As a single agent, weekly vinorelbine achieved impressive results in first line setting [3]. The combination of vinorelbine with 5-fluorouracil achieved high responses rates of 60–64% and a manageable toxicity profile, though the tolerance profile of this regimen depends on the schedule [4–7]. Capecitabine, an oral fluoropyrimidine, that mimics 5-FU, has significant activity as a single agent or in combination with taxanes. The substitution of

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5-FU by capecitabine may improve patient's convenience and comfort. Preclinical data suggests that the combination of vinorelbine and capecitabine is synergistic. Several phase I/II trials have explored this combination in heavily pretreated MBC patients. It has generated promising results and a satisfactory safety profile [8–13].

A phase II study conducted earlier by our group showed that this combination is highly effective in the first-line setting with nearly 70% objective response and 90% clinical benefit. The median progression free survival and overall survival were 10 and 30.4 months, respectively [14].

Docetaxel is an antimicrotubule agent. Its efficacy in MBC has been firmly demonstrated in multiple studies. The use of the weekly regimen maintains higher efficacy with less hematological toxicity and an increase of fatigue, hyperlacrimation, nail toxicity and alopecia. Docetaxel as monochemotherapy is proved to be superior over all other drugs [15, 16].

Two approaches have been used in the treatment of MBC: The "drug dose density" and the "sequential approach". There is no justification to use high-dose chemotherapy in MBC patients outside a clinical trial [17, 18]. In the sequential approach, there is no clear superiority of a second drug given after progression versus a combined therapy in anthracycline-pretreated MBC. However, the sequential approach has the advantage of lowering the hematological side effects while maintaining the anti-tumor activity [19–23].

Based on the above, and on our experience with the association of Vinorelbine and Capecitabine (Navcap), the sequential administration of Navcap (sequence A) followed by Docetaxel (sequence B), dubbed the "NEXT regimen" was proposed for a trial in this study.

Objectives

The primary objective of the study was to evaluate the objective response rate (ORR) in the intent-to-treat population of the NEXT regimen. Secondary objectives were to evaluate the safety profile, the Time Till Progression (TTP), the duration of response and the Overall Survival (OS) of this regimen.

Patients and methods

Patient population

Eligible patients were women at least 18 years old, with histologically proven MBC, irrespective of the Her-2/neu status. Other inclusion criteria were: WHO performance status less than two, at least one bi-dimensionally measurable lesion that had not been irradiated. Previous adjuvant chemotherapy containing anthracycline, taxanes or 5-FU and previous hormonal therapy for adjuvant or metastatic disease were allowed. Participants' life had to be superior to 3 months, and their bone marrow, liver and renal functions adequate. Patients were required to give a written informed consent before study-specific procedures were performed and to agree to comply with the protocol for the duration of the study.

Patients were ineligible if they had local relapse only, prior chemotherapy in the metastatic setting, or had been previously treated with vinca-alcaloid or capecitabine. Patients were also excluded if they had peripheral neuropathy in more than two sites, dysphagia or inability to swallow the tablets, malabsorption syndrome or any disease significantly affecting gastro-intestinal functions that could impede the absorption of capecitabine, other serious illness or medical conditions such as cardiac disease, unstable diabetes, uncontrolled hypercalcemia, significantly active infection, or previous organ allograft. Patients who were pregnant or lactating, who had symptoms suggesting CNS or leptomeningeal metastases, who had required the concurrent use of antiviral agent sorivudine or chemically related analogues, who had participated in another clinical trial with any investigational drug within 30 days prior the study inclusion, who had a history of another malignancy within the past 5 years except cured basal cell carcinoma of the skin or excised carcinoma in situ of the cervix, were also excluded.

Study design

Chemotherapy treatment consisted of Vinorelbine 25 mg/m² administered on days 1 and 8 of a 3 weeks treatment cycle, plus Capecitabine 825 mg/m² twice daily for 14 days, for a daily total of 1,650 mg/m², followed by 7 days of rest. The treatment was pursued for four cycles in absence of progression at which time patients received Docetaxel 25 mg/m^2 per week for 12 consecutive weeks.

Patients progressing within the first two cycles of Navcap received the sequence B (Docetaxel) as a second line treatment. They were subsequently included in the intent-to-treat analysis.

Sample size calculation

The efficacy of the combination as a first-line treatment for MBC was measured as an Overall Objective Response (ORR). The prevalence of success p used for the sample size calculation was therefore equal to ORR/N where *N* was the number of participants.

Fleming's single-stage design [24] was applied for the sample size determination with the following rules:

- The inactivity cut-off is $P \leq 40\%$, while the activity cut-off is $P \geq 60\%$.
- The error rate of the first type (α) was set to 0.05.
- The error rate of the second type (β) was set to 0.20.

Thus the null hypothesis H0: $p0 \leq 40\%$, was tested versus the alternative success hypothesis Ha: $p0 \geq 60\%$, with a desired alpha ≤ 0.05. The required sample size is 40 patients.

Dose modifications

If grade 3 or 4 hematological or non-hematological toxicities occured, a 25% reduction in the dose of the next cycle was recommended and maintained during all next cycles. In sequence B, the first injection of Docetaxel is given as full dosage in case of dose reduction in previous Navcap cycles. If grade 3 hand–foot syndrome occured, treatment was delayed by 1 week. If toxicity was not resolved at that point, Capecitabine would be resumed with 25% dose reduction. The use of G-CSF was permitted.

Study assessments

Baseline assessments were performed in all patients within 21 days before the start of the study treatment. Complete blood counts were done at each chemotherapy administration. Objective responses (OR) were assessed every 9 weeks until progression or less than 9 weeks if early progression was suspected. The best OR achieved, using the standard WHO criteria of tumor response was reported for each patient. TTP was calculated from the date of inclusion in the study to the date of the first documentation of disease progression.

The efficacy analyses were based on the intent-to-treat population. Safety was analyzed in all patients who received at least one cycle of study medication. Adverse events were recorded and graded according to the version 3.0 of the NCI-CTCAE.

Results

Patients characteristics

Between March 2002 and November 2003, 40 MBC patients were enrolled into the study in three centers. The patients' characteristics are summarized in Table 1.

Table 1 Patient's characteristics

Characteristic	No. of patients	%
No. of patients	40	–
Median age (years) (range)	57 (36–80)	
≥65 years old	10	25
Performance status (range)	1 (0–2)	–
ER status		
Positive	17	42.5
Negative	14	35
Unknown	9	22.5
PR status		
Positive	16	40
Negative	15	37.5
Unknown	9	22.5
Her-2/neu status[a]		
0 and 1+	20	50
2+	1	2.5
3+	5	12.5
Unknown	14	35
Prior adjuvant therapy		
Chemotherapy	30	75
Anthra-based	25	62.5
Taxanes-based	4	10
FU-based	21	52.5
None	10	25
Metastatic patients	40	100
Nbre of Metastatic sites		
1	8	20
2	17	42.5
3	9	22.5
4	6	15
Disease free interval in months		
Median (extremes)	29 (0–180)	

[a] Identified by Immunohistochemistry

Response to the NEXT regimen (sequential treatment)

ORs were obtained in 25 pts (62.5%) in the intent-to-treat population (Table 2). An overall clinical benefit (CR + PR + SD) was reached in 75%. These responses were observed in patients with visceral (61.3%) as well as non-visceral metastasis patients (75%).

The ORR was maintained in patients who received prior anthracycline therapy in comparison with patients who had not (68 vs. 57.14%, respectively).

The median TTP was 12.3 months (range 1.5–48 months; 95% CI, 10.05–14.54) (Fig. 1). Twenty-three pts were on maintenance hormonal treatment after achieving response to the NEXT regimen.

The median survival time for all the study population was 35.8 months ranging from 2 to 47 months (Fig. 2). The observed 1, 2 and 3 year survival are 87.5, 57.5 and 35% of patients, respectively.

Response to the Navcap sequence

Forty patients received the Navcap regimen in a median of four cycles delivered per patient. The number of cycles

Table 2 Objective tumor response rate/intent-to-treat population/investigator assessment

	Navcap ($n = 40$)		Under taxotere ($n = 40$)		Sequential treatment ($n = 40$)	
	n	%	*n*	%	*n*	%
Complete response	2	5	5	12.5	5	12.5
Partial response	20	50	20	50	20	50
Objective response Rate	22	55	25	62.5	25	62.5
Stable disease	13	32.5	3	7.5	5	12.5
Progressive disease	5	12.5	12[a]	30	9	22.5

[a] Include patients who did not receive Docetaxel due to early progression or death and who are not evaluable for Docetaxel treatment (6 pts)

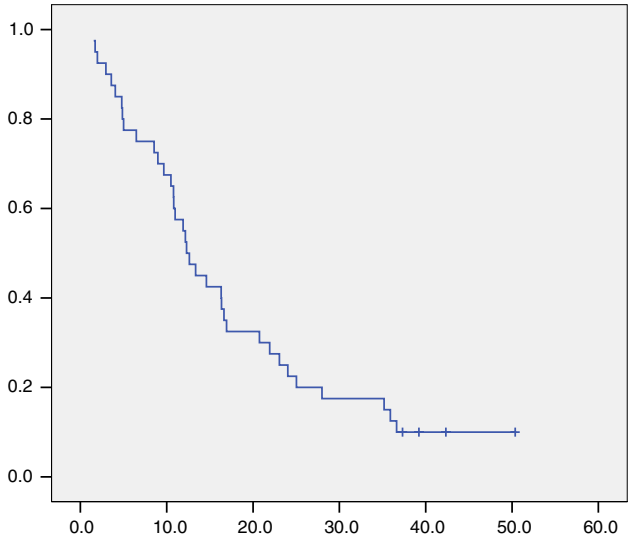

Fig. 1 Kaplan–Meier estimates for time-to-progression-free survival in intent-to-treat patients

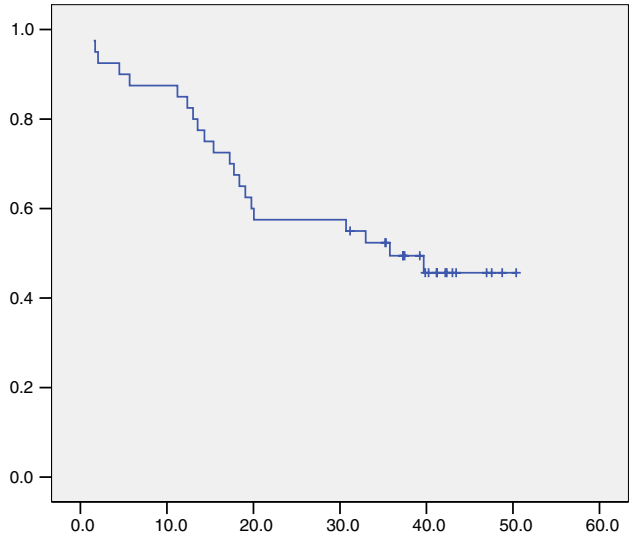

Fig. 2 Kaplan–Meier estimates for time-to-overall-survival in intent-to-treat patients

ranged between 1 and 5. The ORR was observed in 22 pts (55%, IC 38.49–70.74) (Table 2).

Response to the docetaxel sequence

Docetaxel was given weekly to the patients stable or responding to the first sequence of Navcap. Thirty-four patients received Docetaxel after the administration of Navcap and are evaluable for the response. Six patients did not receive Docetaxel. Of those, one patient received Docetaxel following surgery done after four cycles of Navcap to remove the persistent evaluable disease and entered complete remission. Three patients suffered early death, one patient refused to continue and one had an important elevation of liver enzymes due to disease progression and was discontinued.

In the intent-to-treat population, ORR was observed in 25 patients (62.5; 95% CI, 45.8–77.27), SD in 3 (7.5%) and PD in 6 (15%) In the specific population of patients who received Docetaxel and completed the sequence, ORR was 73.53% (95% CI, 55.64–87.12), SD was 8.82% and PD was 17.6% (Table 2).

Dose modification

A total of 151 cycles of vinorelbine (d1, d8) and capecitabine (d1–14) were administered to the 40 patients with a median of four and a range of 1–5 cycles. Capecitabine dose reductions were required for five patients for hematological toxicity, nausea/vomiting and/or mucositis. Vinorelbine doses were reduced in four patients for hematological toxicity. Treatment with Navcap was stopped in one patient after two cycles because she developed febrile neutropenia, mucositis and hand–foot syndrome grade 2. Capecitabine was stopped in one patient for febrile aplasia, mucositis and hand–foot syndrome. One dose of Vinorelbine was omitted for venous toxicity.

Docetaxel was given for a total of 360 perfusions with a median of 12 weeks per patient and a range of 0–12 weeks. Dose reduction was required in one patient. One patient experienced an allergic reaction during the first administration of Docetaxel and refused to continue.

Safety

The most frequent treatment-related adverse events were neutropenia in four patients (10%) and febrile neutropenia in 3 (7.5%). The hematological toxicity due to Docetaxel was moderate: two patients developed thrombopenia grade 3, leucopenia and neutropenia were observed in one patient each (Table 3). The most frequent non-hematological toxicities under Navcap were nausea/vomiting (4 pts), alopecia (3 pts), asthenia (2 pts), diarrhea (1 pt), mucositis (2 pts) and hand–foot syndrome (2 pts) but the incidence of grade 3 and 4 toxicity was low. The most frequent non-hematological toxicities under Docetaxel were nail toxicity (2 pts), neuropathy (2 pts), allergic reaction (1 pt) and gastric toxicity (2 pts) but mild in severity.

Discussion

Metastatic breast cancer is still incurable and the average survival time for treated patients after diagnosis ranges from 18 to 30 months. Cytotoxic chemotherapy is the treatment of choice for patients with hormone receptor-negative tumors or rapidly progressive disease, regardless of hormone receptor status. The combination of chemotherapy and trastuzumab improves DFS and OS rates in patients with HER2-overexpressing metastatic breast cancer. Although anthracycline- and taxane- based regimens are considered most effective, the optimal way to administer them, whether sequentially or in combination remains controversial.

However, the widespread use of anthracyclines and taxanes, especially Paclitaxel, in the adjuvant setting has led to an increasing number of patients presenting with advanced disease that is resistant or intolerant to both drugs. The comparable long-term results of using taxanes either in the first-line or in the second-line setting prompted the search for new agents and new combinations. Different agents, schedules, methods of administration, dose densities and combinations were investigated but the optimal method has yet to be determined.

Table 3 Grade 3 & 4 Navcap and Docetaxel related Hematological toxicities

	Navcap related toxicity		Docetaxel related toxicity	
	N = 40	%	*N* = 35	%
Anemia	1	2.5	1	2.85
Thrombopenia	1	2.5	2	5.7
Neutropenia	4	10	1	2.85
Febrile neutropenia	3	7.5	0	0

Based on synergistic effects of Capecitabine and Vinorelbine, their combination in the first-line treatment of MBC was tested by our group. Objective Response Rates of 70% and clinical benefits of 90% were noted. Median TTP was 10.4 months and median OS 30.4 months. The toxicity profile was acceptable [14].

In this trial, weekly Docetaxel, for 12 consecutive weeks, was introduced sequentially to four cycles of Navcap with the objective of enhancing response rate, maintaining and prolonging the progression-free survival. The sequential addition of Docetaxel yielded to an ORR of 62.5%, a clinical benefit of 75%, a median TTP of 12.3 months and a median OS of 35.8 months. The comparison of the ORR, showed an improvement of 18.5% with the addition of Docetaxel. However, this difference did not reach a statistical significance ($P = 0.12$). The prolonged TTP could be attributed to the fact that 50% of patients received maintenance hormonal treatment, after completion of Navcap followed by Docetaxel, at the physician's discretion and patient's preference.

This weekly regimen allows a full dose delivery at the lowest manageable toxicity (median of 12 Docetaxel perfusions equivalent to 300 mg/m^2 over a 3 months period). Indeed, weekly administration of Docetaxel for MBC is active and feasible [15, 25]. In addition, in a randomized phase II trial ($n = 83$), no difference in response rate was observed between the weekly and the 3 weekly schedules of Docetaxel and a greater grade 3 and 4 toxicity in the 3 weekly arm [26]. More recently, a phase III study compared the Docetaxel weekly versus every 3 weeks regimens in patients with MBC. Patients were randomized to receive Docetaxel at a starting dose of 75 mg/m^2 on day 1 and Docetaxel weekly at a dose of 35 mg/m^2/week for 3 weeks followed by 1 week of rest every 28 days. Docetaxel once every 28 days showed a higher response rate compared to Docetaxel trice every 28 days (35.6 vs. 20.3%) but with a more pronounced toxicity profile. However, no differences in progression free survival or overall survival was observed between both arms [27].

The efficacy of the NEXT regimen was maintained in anthracycline pretreated breast cancer (ORR 68%). The activity was lower in patients with visceral than non-visceral metastasis. It was the same if patients had been primary diagnosed with metastatic disease or if they had relapsed from a previously treated breast cancer. It is noteworthy that more than 50% of patients survived for more than 2 years with the NEXT regimen.

The efficacy of this first line sequential approach compared well with previous reports. The ORR of 62.5% was in the range of response rates reported in phase III and II trials (Table 4; [28–38]). The OS and TTP were also consistent, and in some cases more advantageous than previously published data from trials investigating single-agent, combination

Table 4 Some relevant phase II and III studies in metastatic breast cancer

Trial	Ref.	Year of publication	*n*	Anthracycline pretreated (%)	Line of treatment	RR (%)	OS (mo)	TTP (mo)
Docetaxel vs. Paclitaxel	J Clin Oncol	2005	225 vs. 224	100	1st , 2nd and 3rd	32 vs. 25	15.4 vs. 12.7	5.7 vs. 3.6
Docetaxel/Capecitabine vs. Docetaxel	J Clin Oncol	2002	255 vs. 256	100	1st , 2nd and 3rd	42 vs. 30	14.5 vs. 11.9	6.1 vs. 4.2
Gemcitabine/Paclitaxel vs. Paclitaxel	Proc Am Soc Clin Oncol	2004	267 vs. 262	100	1st	39.3 vs. 25.6	18.5 vs. 15.8	5.4 vs. 3.5
Capecitabine/Docetaxel vs. Docetaxel → Capecitabine	Proc Am Soc Clin Oncol	2006	50 vs. 50	100	1st	68 vs. 40	22 vs. 19	9.3 vs. 7.7
Capecitabine/Docetaxel vs. Capecitabine/ Paclitaxel vs. Capecitabine → Taxanes	Proc Am Soc Clin Oncol	2006	91 vs. 95 vs. 91	100	1st, 2nd and 3rd	74 vs. 65 vs. 46	28.6 vs. 33.1 vs. 31.5	74 vs. 65 vs. 46
Vinorelbine/5FU/Folinic acid	Ann Oncol	1997	45	0	1st	61.5		
Gemcitabine/CDDP	Anticancer Drugs	2006	46	-	1st	81	27.9	14.9
Gemcitabine/Docetaxel	Clin Breast Cancer	2006	39	–	1st	33	15.8	5.8
Vinorelbine/Doxorubicin Vinorelbine/5FU	Oncologist	2001	62 56	0	1st	55 45	21.5 12.4	1.9 7.5
Docetaxel weekly	J Clin Oncol	2000	29	31	1st and 2nd	41	–	–
Bevacizumab/Docetaxel	Clin Cancer Research	2006	77	–	1st and 2nd	52	–	7.5

regimens and sequential approaches (Table 4). As shown above, the higher efficacy of the NEXT combination was accompanied by a predicatble and manageable toxicity profile.

Doses of capecitabine tested in this combination are significantly lower than those reported in the literature and explain the high tolerability of the drug especially the dismal incidence of hand–foot syndrome.

Considering the confirmed efficacy of the combination of Capecitabine and Vinorelbine (Navcap) and the suggested advantage provided by the sequential addition of Docetaxel in terms of efficacy and its low toxicity, a randomized phase II trial has been initiated in Her-2/neu negative MBC patients. Its primary objective is to compare the Navcap regimen to the Navcap followed by Docetaxel over an eight cycles period.

Results will help evaluate the added response rate, time to progression and survival effect of this sequential approach with these drug compared to more classical regimens in Her-2/neu negative MBC patients. In addition to exploring the duration of the treatment, this randomized trial will also assess an optimal use of chemotherapy to lower toxicity even more, and the role of maintenance hormonal or cytotoxic treatments.

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