Breast Cancer Research and Treatment (2019) 176:253–260
https://doi.org/10.1007/s10549-019-05203-1

REVIEW

Vinorelbine plus Capecitabine (Vinocap): a retrospective analysis in heavily pretreated HER2 negative metastatic breast cancer patients

Alfredo Torres[1] · Jeremy L. Ramdial[1] · Luis E. Aguirre[2] · Reshma Mahtani[1] · Charles L. Vogel[1]

Received: 5 March 2019 / Accepted: 13 March 2019 / Published online: 21 March 2019

Abstract

Purpose Metastatic breast cancer is regarded as an incurable entity. In heavily pretreated patients with increasingly limited options for palliative management, ensuring proper quality of life continues is to be an elusive issue. With this in mind, the authors evaluated the efficacy and safety of the Vinorelbine/Capecitabine doublet (VINOCAP).

Patients and methods The investigators retrospectively analyzed a cohort of 67 women with HER2 negative MBC treated at a large breast cancer practice and a local cancer center with Vinorelbine 22.5 mg/m2 IV on days 1 and 8 combined with Capecitabine 1 g PO BID for 14 consecutive days of 21 day cycles. Patients had been treated with an average of 4 prior lines of chemotherapy. Patient characteristics and outcomes were evaluated.

Results A total of 67 patients received VINOCAP, and an additional 2 underwent repeat exposure yielding a cohort of 69. Clinical benefit rate, defined as complete response (CR), partial response (PR) or stable disease ≥ 6 months (SD), was 55.07%. Complete response was seen in 4.34%, PR in 18.8% and SD ≥ 6 months in 31.9%. Median progression-free survival was 6.2 months and overall survival 35.47 months after VINOCAP exposure. The most common grade 3–4 toxicity was neutropenia in 10% of cases. Dose had to be reduced in 18% of cases due to toxicity of any type. The regimen was well tolerated, and serious side effects were uncommon.

Conclusion Vinorelbine/Capecitabine appears to be an active and well-tolerated regimen in women with MBC. In particular, encouraging was the efficacy of VINOCAP as fourth or greater line of chemotherapy.

Keywords Vinorelbine · Capecitabine · Breast neoplasm · Neoplasm metastasis · Hormone-dependent neoplasm · Treatment failure

Background

The overall survival of primary breast cancer has improved significantly over the past 4 decades, as reviewed by Zeichner et al. [1, 2], with a 10 year survival going from 74.8% (1975–1977) to 90.8% (2006–2012) [3]. For early stage breast cancer, advances in surgery and radiation oncology have led to a decrease in the morbidity of loco-regional therapies. In contrast, metastatic breast cancer (MBC) is viewed as essentially incurable with only 2.5% disease-free survival at 15 years [4]. Improvements have occurred but have been modest with median survival from first relapse reported as 26 months (~ 2 years) 1970–1990 [5], and a median survival of 33 months in a recent review [1, 6].

Although essentially incurable, palliative therapies including hormonal, cytotoxic chemotherapy, and targeted therapies used in various sequences, have led to better quality of life and modest increase in 5-year survival [3]. Hormonal treatment remains the mainstay of management for hormonally sensitive MBC, but virtually all such patients will eventually need cytotoxic chemotherapy for palliation and to improve quality of life.

Specifically addressing cytotoxic therapy, historically, single agent therapy is preferred over combination chemotherapy regimens and is our preferred strategy; however, some of the combination therapies have demonstrated

✉ Charles L. Vogel
clvogel@med.miami.edu

[1] Department of Hematology/Oncology, Sylvester Comprehensive Cancer Center, University of Miami Miller School of Medicine, 1192 East Newport Center Drive, Deerfield Beach, FL 33442, USA

[2] Department of Internal Medicine, University of Miami Miller School of Medicine, Jackson Memorial Hospital, Miami, USA

survival benefit over single agent therapy [7]. Some of these results remain controversial because of absence of subsequent crossover to the single agent arm. One such retrospective analysis by Miles et al. [8] suggested that the overall survival benefit of Taxotere and capecitabine over capecitabine alone might have disappeared if there had been such a control arm. In another study comparing monotherapy capecitabine vs. monotherapy vinorelbine versus combination of the two, the combination VINOCAP seemed to double the PFS; however, the study was not designed to compare sequential monotherapy vs. the combination [9]. A recent Cochrane review showed that there is no difference in overall survival between combination and sequential chemotherapy, and combination therapy was associated with higher rates of neutropenic fever [10]. While the VINOCAP combination was not included in this review, the reader is referred to the comprehensive VINOCAP review by Petrelli et al. [11].

The purpose of this paper is to present the results of a highly effective minimally toxic combination regimen that we have used for over two decades. The use was prompted by in vitro studies showing upregulation of thymidine phosphorylase by vinorelbine to improve capecitabine effectiveness [12–15]. We briefly described, in abstract form, the first published experience with this combination in 1999 [16]. Aside from the aforementioned advantages, the drugs also have different mechanisms of action and both are well tolerated and do not cause alopecia.

Based on clinical response noted by our group, we conducted a retrospective study, evaluating clinical efficacy and toxicity in women with MBC treated with VINOCAP used at doses modified from standard doses for each agent. While we have treated patients at all lines of cytotoxic therapy, VINOCAP was usually used in the salvage setting and our patients received an average of 4 lines of prior chemotherapy.

Patients and methods

Study population

We retrospectively analyzed over 5000 charts of all women treated first in a large breast cancer-specific private practice and then by Dr. R. Mahtani and Dr. C. L. Vogel at the Deerfield Beach satellite of Sylvester Comprehensive Cancer Center. Details of the entire chart review were summarized in prior publications [1, 17]. Sixty-seven patients with HER-2 negative MBC were identified, and their characteristic were summarized in Table 1. In general, initial patients were chosen for VINOCAP because of their heavily pretreated status. Pretreatment evaluation usually included CBC, CMP, CEA CA15.3 and either PET-CT or CT scans of chest, abdomen and pelvis with contrast and bone scan. Appropriate

Table 1 Patient characteristics (67 patients)

	N	%
Median age (range), years	48 (28–76)	72
Race		
White	35	52
Black	5	8
Other	4	6
Unknown	23	34
Ethnicity		
Non-Hispanic	47	70
Hispanic	10	15
Unknown	10	15
ECOG		
0	40	59.7
1	10	14.9
2	5	7.4
> 2	12	17.9
Molecular subtype		
ER	(+) 51	76
PR	(+) 31	46
Her2	(−) 67	100
Menopause status		
Premenopause	33	50
Perimenopause	7	10
Postmenopause	25	37
Unknown	2	3
Adjuvant chemotherapy	43	60
Prior hormonal therapy	38	53
Previous chemotherapy		
Taxanes	33	49
Anthracyclines	23	34
Other	16	24
Prior exposure to Navelbine or Capecitabine	6	9
Lines of chemotherapy prior to VINOCAP (lines of treatment)		
1 line therapy	9	13
2 lines therapy	17	24.6
3 lines therapy	11	15.9
4 lines therapy	8	11.6
> 4 lines therapy	24	34.8
Lines of hormonal therapy prior to VINOCAP		
1 line therapy	18	26
2 lines therapy	7	10
3 lines therapy	5	7
≥ 4 lines therapy	5	7
Uncertain	32	47.8
Dominant site of metastases		
Viscera	47	70
Bone	11	16.5
Soft tissue	9	13
Median disease-free interval in months		
Time from surgery to recurrence	48 months	
Time from recurrence to initiation of combo	29 months	

Retrospective data analysis. Line of therapy refers to prior systemic regimens of chemotherapy before initiation of VINOCAP

Two patients treated twice with VINOCAP were not included in this table ($n = 67$)

imaging was performed every 2–3 courses of therapy (as defined below) with the above blood tests performed at the start of each course of treatment. Approval from the University of Miami Institutional Review Board was obtained prior to initiation of data collection.

As noted in Table 1, the majority of our patients were white, non-Hispanic, premenopausal women. The median age was 48 years (range 28–76). The dominant site of metastasis was visceral in 70%, osseous in 16%, and soft tissue in 13% of patients. Most of them were originally treated with adjuvant chemotherapy (60%) and/or hormonal therapy (53%). Seventy-six percent were estrogen receptor positive, and the majority had ECOG performance scores of zero or one.

The median disease-free interval from the date of surgery to recurrence was 48 months. The median time from diagnosis of metastasis to initiation of VINOCAP was 29 months (1–81 months). Patients received a median of four lines of chemotherapy for metastatic disease prior to the initiation of VINOCAP. In 35% of patients, VINOCAP was given after the fourth line of chemotherapy. As will be seen in Fig. 1, the major analysis is based on prior lines of cytotoxic chemotherapy; however, we were unable to appropriately capture the number of lines of hormonal therapy received by these patients. Hence the numbers of lines of therapy for metastatic disease would likely be higher.

Treatment

All patients received VINOCAP. Capecitabine doses were never given according to FDA approved dosing since significant dose reductions have become the U.S. norm since serious toxicities are generally encountered at the FDA approved dose of capecitabine (1250 mg/m^2 twice per day for 14 days every 21 days). Capecitabine was given at 1 g total dose twice a day at the end of the morning and evening meals for 14 days with a seven day period before the next cycle. This single agent capecitabine dosing was validated in the publication by Ambros et al. [18]. Vinorelbine dose was 22.5 mg/m^2 administered as an intravenous injection or infusion over 6 to 10 min on days 1, 8, and 15 of a 21 day cycle. Because of inordinate hematologic toxicity on day 15 of the above-mentioned schedule, most patients in the study population received Vinorelbine on day 1 and 8. Doses were occasionally reduced from the usual starting doses for toxicities.

Response criteria

The evaluation of response was based on approximations of elements similar to RECIST criteria where possible but the treating physician using physical examination, serum tumor markers, and imaging often used clinical judgment especially for patients with non-measurable disease. Tumor marker changes were never used to determine disease response without confirmatory imaging changes. Imaging modalities used to assess progression of disease were computerized tomography (CT), magnetic resonance (MRI) and positron-emission tomography (PET-CT). Clinical response was defined using several elements to gauge patient's overall status. Complete response (CR) was defined as the absence of clinical, laboratory and radiographic evidence of malignant tissue. Partial response (PR) was defined as definite decrease of 50% or greater in disease burden on imaging when available. Stable disease (SD) was defined as the absence of progressive disease for at least 6 months. Patients experiencing stable disease for less than 6 months were considered as having progressive disease (PD). PD was also defined as increase in disease burden shown by imaging modalities, histological confirmation of a new lesion or clinical deterioration as a consequence of MBC in the opinion of the attending physician. The clinical benefit rate was defined as CR, PR or SD ($\geq$6 months). Response rate (RR) was defined as CR or PR in patients with measurable disease. Progression-free survival (PFS), defined as the time from initiation of combination therapy to disease progression, and overall survival (OS) defined as the time from initiation of VINOCAP to death were calculated as well. Overall survival from diagnosis of primary cancer to death and from diagnosis of metastatic disease to death were also calculated. Patients were treated until there was objective evidence of disease progression, inordinate toxicity or patients' desire to discontinue therapy.

Toxic effects were graded according to the National Cancer Institute Common Toxicity Criteria for adverse Events 2.0 version. This modality was used given that a vast majority of patients were evaluated during the release of the 2.0 version [19]. The decision to reduce the initial dose or to discontinue therapy was at the discretion of the attending physician. Some patients were treated based on a strategy of once a week filgrastim to maintain the dose intensity of Navelbine if difficulty was encountered administering day 8 chemotherapy because of neutropenia [36, 37].

Statistical analysis

Statistical analysis was performed using Stata 13. StataCorp. 2013 Stata Statistical Software: Release 13. College Station, TX: StataCorp LP. We used descriptive statistics to summarize patient and disease characteristics and clinical outcomes. Survival analysis consisted of Overall unadjusted survival and progression-free survival was visualized using the Kaplan–Meier method with 95% confidence intervals (95% CIs).

Literature review

A literature review was performed by searching the English literature using Pubmed (National Library of Medicine, Bethesda, MD) and Trip Database for the period January 1999 to May 2016. We used the terms *capecitabine, vinorelbine, and breast cancer*. We narrowed the search by using *clinical trial* as the article type. Relevant identified manuscripts were included. Studies were excluded if vinorelbine was not given intravenously (IV). In addition, we reviewed references cited in all the manuscripts to identify additional published clinical trials [20–24].

Results

Patient characteristics

Charts from over 5000 patients were reviewed, of which 315 women with MBC and Her2 negativity were identified. Excluded patients were as follows: men, locally relapsed breast cancer, other malignancy, patients clinically and continuously disease-free after primary local regional therapy, one-time consultations, and patients primarily treated elsewhere. We found 67 women with MBC that were Her2 negative, who were treated with the combination of capecitabine and vinorelbine (VINOCAP). Two patients among the 67 had two separate exposures resulting in an evaluable sample size of 69. Unfortunately, data collection on prior hormonal exposure in metastatic disease was not appropriately captured in our study population lacking information in 34 out of 69 patients.

Efficacy

Drug efficacy was evaluated in patients with measurable (32 patients) and evaluable but not measurable disease (35 patients). The overall response rate for the 69 exposures was 23.19% among those with measurable disease. Since many patients had evaluable, but not, measurable tumor, clinical benefit (as previously defined) was used as an end point to capture the entire patient population. Clinical benefit was 55.07%. The PFS on VINOCAP was 6.2 months (1–54 months), and overall survival of our entire cohort was 35.47 months defined from initiation of VINOCAP until date of death. In the entire cohort (67 patients and 69 total exposures) evaluated for clinical benefit, 4.34% had a complete response, 18.84% had a partial response, and 31.9% had stable disease greater than 6 months. The greatest clinical benefit was seen in the 24 patients who received the combination as 4th line or greater line of therapy with 6/24 (26.2%) having an objective response (CR or PR), and 15/24 (62.5%) deriving clinical benefit. Figure 1 shows the clinical benefit as a function of prior lines of chemotherapy. Figure 2 depicts the clinical benefit derived from treatment with VINOCAP in the form of a Swimmer plot.

Two patients were exposed to the combination for a second time as they had documented good response at an earlier date. Their subsequent exposures were 13th line and 14th line, respectively, and the duration of disease control for these 2 patients was 33 and 12 months for the first patient, and 35 months and 4 months for the second. Time interval between first and second exposure was 3 years in the patient that received VINOCAP as the 14th line and 1 year

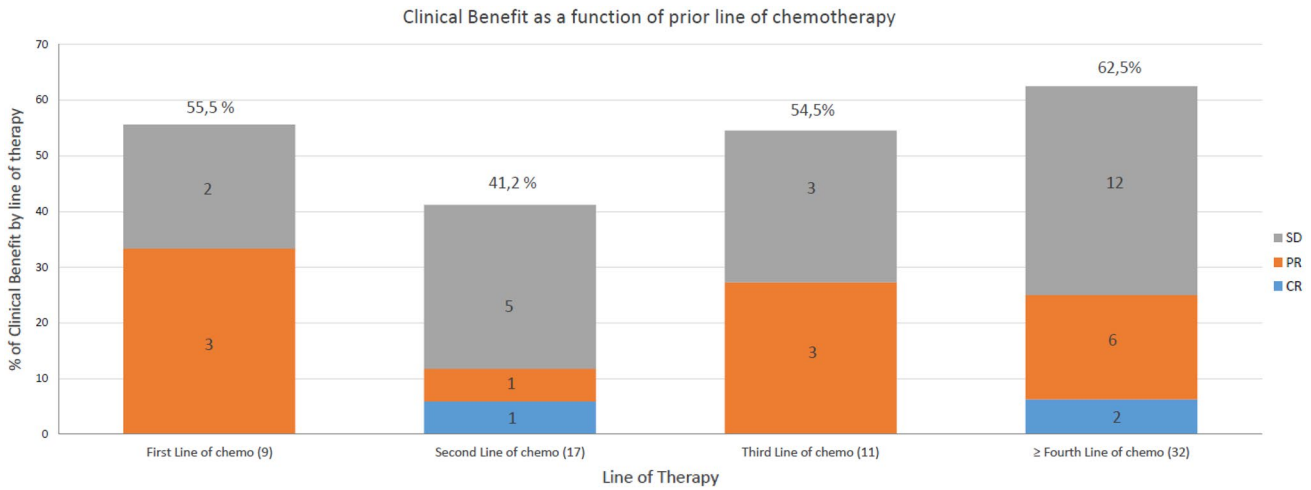

Fig. 1 Clinical benefit as a function of prior line of chemotherapy. Each color represents the type of observed response: CR (complete response) is depicted in blue, PR (partial response) in orange, and SD (stable disease for more than 6 months) in grey. Percentages on top of each stack depict the amount of clinical benefit seen with VINOCAP as a function of CR, PR and SD rates versus total in subgroup (in parentheses)

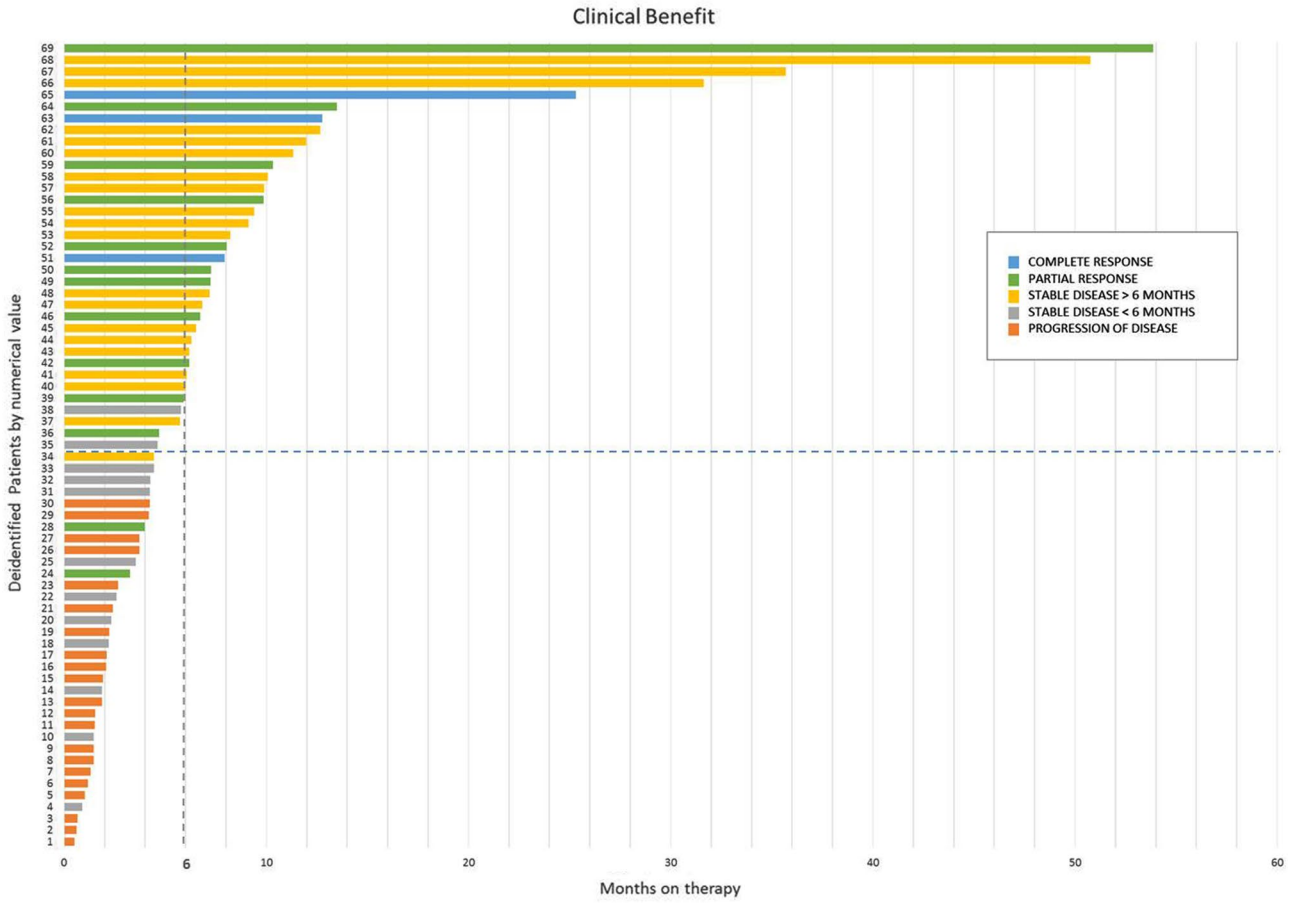

Fig. 2 Clinical benefit: Swimmer plot on duration of therapy. De-identified patients are arranged according to duration of treatment on VINOCAP from short (15 days) to long (53.87 months). Each color represents the type of response exhibited in each case. Dotted line represents median duration of disease

9 months in the patient that received VINOCAP as 13th line of therapy.

It is important to note that all data were analyzed using 69 exposures except for overall survival, where the total number was 67.

Adverse events (Tables 2, 3)

Most common side effect were G1-2 anemia and neutropenia followed by constipation. The most common grade 3–4 toxicity in our cohort was neutropenia, occurring in 7 patients (10%). Other grade 3–4 toxicities were anemia, diarrhea, constipation, palmar-plantar erythrodysesthesia. Dose had to be reduced in 18% of the patients due to toxicity as detailed in Table 2. Most patients were able to tolerate the regimens at full dose. Alopecia, which is a common concern among patients exposed to chemotherapy, was not seen with this regimen. Some patients starting Vinocap with alopecia from preceding regimens actually started regrowing hair during therapy.

Table 2 Toxicity

Toxicity	G1–2 # (%)	G3–4 # (%)
AEs non-hematologic	27 (39.7)	7 (46.7)
Diarrhea	3 (4.4)	2 (13.3)
Constipation	10 (14.7)	3 (20)
Stomatitis	1 (1.5)	0 (0)
PPE	9 (13.2)	2 (13.3)
Increased LFTs	4 (5.9)	0 (0)
AEs hematologic	41 (60.3)	8 (53.3)
Anemia	27 (39.7)	1 (6.7)
Neutropenia	14 (20.6)	7 (46.7)
Total AEs	68 (100)	15 (100)

Total adverse events reported: 83. Grade 1/Grade 2 AEs: 68 cases (81.9%). Grade 3/Grade 4 AEs: 15 cases (18.1%)

1 patient did not experience any toxicity

Table 3 Alterations in regimen due to toxicity (n = 69)

Event	# (%)
Required filgrastim	15 (21.7)
Number of patients with Navelbine dose reductions	12 (17.4)
Number of patients that had Navelbine dose held	28 (40.6)
Number of patients that had Capecitabine held	6 (8.7)

Literature review results (Table 4)

We found 18 published phase I and phase II clinical trials that used the combination of intravenous vinorelbine and capecitabine [12, 25–34]. They reported a PFS ranging from 3 to 12 months and an ORR ranging from 14 to 70%. In most studies, doses of both drugs were higher than those used in this series.

In the meta-analysis performed by Petrelli et al. [11], 27 studies including Phase 2 and Phase 3 trials were evaluated and pooled estimates of ORR, PFS, and OS were calculated. Their RR was between 41–52%, slightly better than 23% found in our cohort but not much different from our clinical benefit rate. Median PFS was 7.3 months, and median OS was 22.3 months, very similar to our cohort where PFS was 6.2 months and OS 35.45 months.

Table 4 Literature review Table

Authors	No. of patients	PFS	ORR (%)
PHASE II Published studies of the combination of vinorelbine and capecitabine			
Zhang et al.	30	7.2 (6.4-8)	60
Lv et al.	98	12 (10.5–13.5)	61.20
Liao et al.	18	4.9 (3.4–6.3)	14.80
Mao et al.	50	8.2 (7.5–8.8)	26
Fan et al.	72	7.7 (5.5–10)	45.80
Lorusso et al.	38	6.4 (1–13)	37
Orphanos et al.	39	N/A	53.90
Esteves et al.	31	7.6 (5.7–9.8)	49
Hess et al.	70	4.3 (3.5-6)* 7 (4.1–8.3)**	42.60* 56**
Ghosn et al.	30	10 (7.6–13.6)	70
Ahn et al.	44	5.3 (1.8–30)	50
Phase I studies of the combination of vinorelbine and capecitabine			
Hess et al.	36	5.3 (2.7–7.8)* 4.5 (3.3–6.9)**	53.00* 48**
Favier et al.	10	N/A	N/A
Nole et al.	49	7.4 (2-12.6)	37
Lorusso et al.	18	3 (1–8)	38
Phase I/II studies of the combination of Vinorelbine and Capecitabine			
Strada et al.	42	8.2 (7.5–8.8)	73.10
Schott et al.	25	N/A	30
Welt et al.	33	8 (4.3–11.7)	55

*Bone

**No bone

Discussion

While there is great enthusiasm and hope for future benefits in MBC from next generation sequencing, vaccines, immunotherapies and new targeted agents, many of these trials are still investigational. Thus, until such trials reach maturity, hormonal therapy and chemotherapy remain the mainstay of treatment for Her2 negative MBC.

This report documents the use of a highly effective, minimally toxic, combination chemotherapy regimen used in patients with MBC, a disease known to have a guarded prognosis and where cure has proven elusive. We documented the use of this combination including toxicity and best clinical response in our patient population. In particular, encouraging was the efficacy of VINOCAP in patients treated as 4th or greater line of chemotherapy with a clinical benefit rate of 62.5%. Also interesting was the use of VINOCAP at a subsequent time in two patients, with good response in one of the two and similar toxicity profiles.

The PFS of 6.2 months and clinical benefit rate of 55.07% in our patients with a favorable toxicity profile and no alopecia makes this an attractive option for salvage chemotherapy in patients felt to need combination rather than sequential single agent therapy.

Capecitabine in this combination was used according to the low dose regimen previously described by Ambros et al. [18]. Likewise, supportive of this low dose regimen is the retrospective analysis of capecitabine done by Leonard et al. [35] who recognized the high rate of dose reductions and cycle delays in a retrospective analysis when used at higher doses.

Although the usual dose for Vinorelbine is 25–30 mg/m^2 intravenous on day 1 and 8 the actual delivered dose in most clinical trials after dose reductions for neutropenia is 22.5 mg/m^2. Further, the use of single dose filgrastim prior to day 8 as per a previously reported series [36, 37] was sometimes helpful in maintaining dose intensity.

Publishing this present series in 2018 may seem anachronistic in this era when personalized medicine, targeted therapies and immunotherapies dominate the investigational landscape. On the other hand, our patients with MBC continue to be treated with conventional therapies sequentially for palliation and prolongation of life. While overall survival of ≥ 5 years is seen, the percentage of such patients is only 26.9% [3]. For patients with triple negative or hormonal refractory, luminal MBC, new cytotoxic agents or novel drugs already in our current armamentarium could still be of practical value.

The major strength of this paper lies in presenting the effectiveness and tolerability of an old regimen, VINOCAP, in a heavily pretreated population of MBC patients. The major weakness was our inability to capture the prior hormonal therapies received by our patients. On the other hand, it is more than likely that inclusion of prior hormonal therapies in our analysis would have made our population even more heavily pretreated. Others may question what the sequential use of these agents may show, on the other hand, even the clinical trials potentially showing a survival benefit of combination vs. sequential agents did not include an arm of sequential therapy (Taxatere/Capecitabine vs. single agent Capecitabine, Ixabepilone/Capecitabine vs. Capecitabine, Gemcitabine/ Paclitaxel vs. Paclitaxel, Paclitaxel/Bevacizumab vs. Paclitaxel).

While the authors fully endorse sequential agent over combination chemotherapy when that modality is needed in MBC, more aggressive tumor presentations can call for the use of combination of cytotoxic agents. Innumerable doublets and triplets have been studied and reviewed for MBC [7]. We feel that VINOCAP could be equivalent to other, usually more toxic doublets with less toxicity and without alopecia. Although comparison of VINOCAP against other salvage combinations will never be done because of many other more innovative palliative strategies to be studied, we feel this combination is worthy of clinical consideration when faced with a patient with MBC in need of combination chemotherapy.

Conclusion

The combination of Vinorelbine and Capecitabine appears to be an active and well-tolerated regimen in women with MBC. A PFS of 6.2 months and clinical benefit in > 50% of cases especially when used after ≥ 4 lines of chemotherapy with no reported instances of alopecia seem particularly compelling arguments that should warrant consideration in this patient population. Consequently, Vinocap may serve as an additional alternative in heavily pretreated patients confronting increasingly limited options for palliative management with preservation of quality of life.

Acknowledgements Alfredo Torres and Jeremy Ramdial are fellows at the Department of Hematology/Oncology at the University of Miami, Jackson Memorial Hospital and Sylvester Comprehensive Cancer Center. Luis E. Aguirre is a resident physician at the Department of Internal Medicine at the University of Miami and Jackson Memorial Hospital. Reshma Mahtani works as associate professor of Hematology/Oncology at the University of Miami Sylvester Comprehensive Cancer Center located in Deerfield Beach, Florida. She is an Editorial Board Member for The Breast Journal. Charles L. Vogel works as Professor of Hematology/Oncology at the University of Miami Sylvester Comprehensive Cancer Center located in Deerfield Beach, Florida.

Author contribution Conception/design: Jeremy Ramdial, Alfredo Torres, Luis E. Aguirre, Charles Vogel. Provision of study material or patients: Charles Vogel, Reshma Mahtani, Jeremy Ramdial. Collection and/or assembly of data: Jeremy Ramdial, Alfredo Torres, Luis E. Aguirre, Charles Vogel, Reshma Mahtani. Data analysis and interpretation: Luis E. Aguirre, Jeremy Ramdial, Alfredo Torres, Charles Vogel. Manuscript writing: Alfredo Torres, Jeremy Ramdial, Luis E. Aguirre, Charles Vogel. Final approval of manuscript: Charles Vogel.

Compliance with ethical standards

Conflict of interest Reshma Mahtani serves as consultant for Pfizer, Lilly, Novartis, Amgen, Celgene, Eisai, Agendia, PUMA biotechnology and Biotherapeutics Inc. Charles L. Vogel serves as consultant/advisor for PUMA biotechnology and ADGERO biopharmaceuticals. Alfredo Torres, Jeremy L. Ramdial and Luis E. Aguirre declare that they have no conflict of interest. The authors certify that they have no affiliations with or involvement in any organization or entity with any financial interest, or non-financial in the subject matter or materials discussed in this manuscript.

Ethical approval All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards.

Informed consent Informed consent was obtained from all individual participants included in the study.

References

1. Zeichner SB et al (2015) Defining the survival benchmark for breast cancer patients with systemic relapse. Breast Cancer (Auckl) 9:9–17
2. Zeichner SB, Terawaki H, Gogineni K (2016) A review of systemic treatment in metastatic triple-negative breast cancer. Breast Cancer (Auckl) 10:25–36
3. Breast Cancer (2016) CSR 1975–2013—sect_04_breast.pdf. http://seer.cancer.gov/csr/1975_2013/results_merged/sect_04_breast.pdf
4. Greenberg PA et al (1996) Long-term follow-up of patients with complete remission following combination chemotherapy for metastatic breast cancer. J Clin Oncol 14(8):2197–2205
5. Vogel CL et al (1992) Survival after first recurrence of breast cancer. The Miami experience. Cancer 70(1):129–135
6. Miles D, von Minckwitz G, Seidman AD (2002) Combination versus sequential single-agent therapy in metastatic breast cancer. Oncologist 7:13–19
7. Cardoso F et al (2009) International guidelines for management of metastatic breast cancer: combination vs sequential single-agent chemotherapy. J Natl Cancer Inst 101(17):1174–1181
8. Miles D et al (2004) Survival benefit with capecitabine/docetaxel versus docetaxel alone: analysis of therapy in a randomized phase III trial. Clin Breast Cancer 5(4):273–278
9. Chan A, Verrill M (2009) Capecitabine and vinorelbine in metastatic breast cancer. Eur J Cancer 45(13):2253–2265
10. Dear RF et al., Combination versus sequential single agent chemotherapy for metastatic breast cancer. Cochrane Database Syst Rev, 2013(12): p. CD008792
11. Petrelli F et al (2016) Vinorelbine with capecitabine, an evergreen doublet for advanced breast cancer: a systematic literature review

and pooled-analysis of phase II-III studies. Clin Breast Cancer 16(5):327–334
12. Zhang J et al (2013) Vinorelbine and capecitabine in anthracycline- and/or taxane-pretreated metastatic breast cancer: sequential or combinational? Cancer Chemother Pharmacol 71(1):103–113
13. Loo WT, Sasano H, Chow LW (2007) Effects of capecitabine and vinorelbine on cell proliferation, metabolism and COX2 and p16 expression in breast cancer cell lines and solid tumour tissues. Biomed Pharmacother 61(9):596–600
14. Goa KL, Faulds D (1994) Vinorelbine. A review of its pharmacological properties and clinical use in cancer chemotherapy. Drugs Aging 5(3):200–234
15. Marty M et al (1992) A review of the antitumour activity of vinorelbine in breast cancer. Drugs 44:29–35; discussion 66–9
16. Domenech G, Perez A, Vogel C, Vinorelbine/capecitabine (VINOCAP) combination remission induction therapy for metastatic breast cancer. Pro Am Soc Clin Oncol. 2001
17. Zeichner SB et al (2015) Survival of patients with de-novo metastatic breast cancer: analysis of data from a large breast cancer-specific private practice, a university-based cancer center and review of the literature. Breast Cancer Res Treat 153(3):617–624
18. Ambros T et al (2014) A retrospective study evaluating a fixed low dose capecitabine monotherapy in women with HER-2 negative metastatic breast cancer. Breast Cancer Res Treat 146(1):7–14
19. Cazzaniga ME et al (2014) Efficacy and safety of the all-oral schedule of metronomic vinorelbine and capecitabine in locally advanced or metastatic breast cancer patients: the phase I-II VICTOR-1 study. Int J Breast Cancer 2014:769790
20. Hess D et al (2004) Capecitabine and vinorelbine in elderly patients (> or = 65 years) with metastatic breast cancer: a phase I trial (SAKK 25/99). Ann Oncol 15(12):1760–1765
21. Hess D et al (2007) Capecitabine and vinorelbine as first-line treatment in elderly patients (> or = 65 years) with metastatic breast cancer. A phase II trial (SAKK 25/99). Oncology 73(3–4):228–237
22. Ahn JH et al (2004) Capecitabine and vinorelbine in patients with metastatic breast cancer previously treated with anthracycline and taxane. J Korean Med Sci 19(4):547–553
23. Favier L et al (2008) Results of a phase I trial of intravenous vinorelbine plus oral capecitabine as first-line chemotherapy of metastatic breast cancer. Breast 17(1):36–41
24. Nole F et al (2006) Capecitabine/vinorelbine: an effective and well-tolerated regimen for women with pretreated advanced-stage breast cancer. Clin Breast Cancer 6(6):518–524
25. Lv H et al (2014) Efficacy of capecitabine-based combination therapy and single-agent capecitabine maintenance therapy in patients with metastatic breast cancer. Chin J Cancer Res 26(6):692–697
26. Liao Y et al (2013) Acceptable but limited efficacy of capecitabine-based doublets in the first-line treatment of metastatic triple-negative breast cancer: a pilot study. Chemotherapy 59(3):207–213
27. Mao W et al (2011) Second-line combination chemotherapy with vinorelbine and capecitabine in patients with advanced breast cancer previously treated with anthracyclines and/or taxanes. Chemotherapy 57(1):71–76
28. Fan Y et al (2010) Prospective study of vinorelbine and capecitabine combination therapy in Chinese patients with metastatic breast cancer pretreated with anthracyclines and taxanes. Chemotherapy 56(4):340–347
29. Lorusso V et al (2003) A phase I study of capecitabine in combination with vinorelbine in advanced breast cancer. Clin Breast Cancer 4(2):138–141
30. Lorusso V et al (2010) Intravenous versus oral vinorelbine plus capecitabine as second-line treatment in advanced breast cancer patients. A retrospective comparison of two consecutive phase II studies. Breast 19(3):214–218
31. Orphanos G et al (2010) A Phase II trial of the combination of vinorelbine and capecitabine as second-line treatment in metastatic breast cancer previously treated with taxanes and/or anthracyclines. J Cancer Res Clin Oncol 136(1):115–121
32. Ghosn M et al (2006) Phase II trial of capecitabine and vinorelbine as first-line chemotherapy for metastatic breast cancer patients. Anticancer Res 26(3B):2451–2456
33. Estevez LG et al (2008) A Phase II study of capecitabine and vinorelbine in patients with metastatic breast cancer pretreated with anthracyclines and taxanes. Clin Breast Cancer 8(2):149–154
34. Lorusso V et al (2006) Oral vinorelbine plus capecitabine (oral vincap) combination in patients with advanced breast cancer (ABC). A phase II study of the GOIM (Gruppo Oncologico dell'Italia Meridionale). Ann Oncol 17(Suppl 7):vii15–7
35. Leonard R et al (2011) Dose-adjusting capecitabine minimizes adverse effects while maintaining efficacy: a retrospective review of capecitabine for metastatic breast cancer. Clin Breast Cancer 11(6):349–356
36. Ellis GK et al (1999) Infusional paclitaxel and weekly vinorelbine chemotherapy with concurrent filgrastim for metastatic breast cancer: high complete response rate in a phase I-II study of doxorubicin-treated patients. J Clin Oncol 17(5):1407–1412
37. Livingstone R et al (1997) Dose-intensive vinorelbine with concurrent granulocyte colony-stimulating factor support in paclitaxel-refractory metastatic breast cancer. J Clin Oncol 15(4):1395–1400