Vinorelbine in Combination with Leucovorin and 5-Fluorouracil Vs Single Agent Docetaxel as First-Line Therapy in Metastatic Breast Cancer Pre-Treated With Anthracyclines

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Abstract

Objective: The purpose of the study is to compare the efficacy and tolerability of vinorelbine (VNB) plus 5-fluorouracil (5-FU) and leucovorin (LV) combination chemotherapy (VLF) with single agent docetaxel given as first-line therapy to patients with metastatic breast cancer (MBC) after failure of anthracycline based chemotherapy.

Patients and methods: Sixty patients with MBC previously treated with an adjuvant anthracycline were enrolled. Thirty one patients were treated with docetaxel 100mg/m^2 every 3 weeks and 29 patients were treated with a combination of VNB 25mg/m^2 plus LV 30mg/m^2 followed by 5-FU 600 mg/m^2 infused over 24h on days 1 and 8 of each 3-week cycle.

Results: The overall response rate was 51.6% and 44.8% (p=0.6) in the docetaxel and VLF groups respectively. Three (9.7%) complete responses and 13 (41.9%) partial responses occurred with docetaxel, while 2 (6.9%) complete responses and 11 (37.9%) partial responses occurred with VLF. Median time to disease progression (9Vs 8.5 months) and median overall survival (18 Vs 16 months) did not differ significantly between the docetaxel and VLF arms respectively. Severe toxicity was uncommon with higher incidence of neutropenia, skin disorders and peripheral edema with docetaxel, whereas VLF combination resulted in more thrombocytopenia and gastrointestinal disorders.

Conclusions: These two regimens were active for MBC, while there appeared to be evidence in favor of docetaxel not reaching statistical significance. The safety profiles of both therapies are manageable and tolerable.

Key Words: Metastatic breast cancer – Dooetaxel – Vinorelbine – 5-Fluorouracil.

Introduction

BREAST cancer is the most prevalent malignancy globally and the leading cause of cancer related death in women, with more than a million newly diagnosed cases occurring worldwide annually [1]. Furthermore, it is estimated that 30-75% of patients undergoing surgery and adjuvant treatment will develop recurrent disease [2]. Metastatic breast cancer (MBC) is essentially incurable with standard therapy and patients with MBC have a median survival of about 2 years after metastases have been detected. As a consequence, treatment goals are to improve symptoms, prolong survival, and maintain or improve quality of life [3]. Despite the introduction of new, active, chemotherapy agents as well as drugs with a novel mechanism of action, such as Herceptin, the treatment of MBC remains a challenge. The ideal regimen in this situation would be effective, well tolerated, easy to administer, and inexpensive. Although many effective regimens have been reported, none is ideal and continued research is needed. Furthermore, when active drugs are discovered, they commonly become used in adjuvant therapy and are therefore less appropriate for use in metastatic disease [4].

Docetaxel is a semisynthetic taxane, a class anticancer agents that binds to β-tubulin and hyperstabilize the microtubules, thereby inducing cell cycle arrest and subsequent apoptosis [5,6]. Several phase 3 trials confirmed the activity of docetaxel in the first-line treatment of and in anthracycline-resistant MBC [7,8]. Single agent docetaxel and docetaxel-based regimens demonstrated clinical activity in stage II to III breast cancer [9-11] and were later approved for the adjuvant treatment of early high-risk breast cancer [12]. It is important to note that the widespread use of anthracyclines and taxanes in the adjuvant setting has led to an increasing number of patients presenting with advanced disease that is resistant to both drugs. In this population, treatment options remain controversial because no standard chemotherapy has been defined [13].
Vinorelbine (VNB) is a semisynthetic vinca alkaloid that inhibits tubulin polymerization, thereby impairing the function of mitotic spindles. Intravenous (iv) VNB has been widely investigated in the treatment of MBC. Response rates of 35-50% have consistently been demonstrated for first-line single-agent VNB [14-18]. The good tolerance profile of iv VNB has enabled its use in combination with other cytotoxic agents active against MBC. Among them, 5-fluorouracil (5-FU) is a potentially relevant candidate agent. 5-fluorouracil could inhibit thymidylate synthetase (TS) and prevents the formation of thymidine monophosphate (dTMP) which is an important precursor of thymidine triphosphate (dTTP), one of the four deoxynucleotides required for DNA synthesis [19,20]. Biochemical modulation of 5-FU by the addition of leucovorin (LV) potentiates the cytotoxic effects of 5-FU by increasing the binding of activated 5-FU to TS [20].

Objective:

The purpose of the study is to compare the efficacy and tolerability of VNB plus 5-FU and LV (VLF) combination with single agent docetaxel given as first-line therapy to patients with MBC after failure of anthracycline-based chemotherapy.

Patients and Methods

Eligibility criteria:

To be eligible for the study, patients had to be ambulant female <70 years old, displayed Eastern Cooperative Oncology Group (ECOG) status of 0-2 and have histological or cytological diagnosis of MBC. The tumors were required to be measurable or evaluable. All patients should have received and failed from postmastectomy adjuvant anthracycline-based chemotherapy given beyond 6 months before study enrolment. Patients were classified as anthracycline-sensitive (relapse more than 12 months after adjuvant chemotherapy) or resistant (relapse within 12 months following adjuvant chemotherapy). Other inclusion criteria were adequate haematological function (neutrophil ≥ 1.5x10^9/l, haemoglobin ≥ 10gm/dl and platelets ≥ 100x10^9/l), adequate renal function defined as a serum creatinin concentration < 1.5x upper limit of normal (ULN), adequate hepatic function defined as total bilirubin, asparate and alanine aminotransferase < 1.5x ULN and an informed consent obtained from each patient before study treatment. Exclusion criteria were: Prior palliative chemotherapy, CNS involvement, bone metastases; carcinoma-matus lymphangitis of the lung or serous effusion as the only sites of disease, previous or current malignancies and medically unstable or any severe concomitant conditions.

Patient evaluation:

Pretreatment evaluation consisted of a complete medical history, physical examination, complete blood counts, biochemistry profile, ECG, measurement of all tumor associated lesions by chest X-ray completed by chest computed tomography (CT) scan if lung metastases, liver ultrasound completed by abdominal CT scan if liver metastases and a bone scintigraphy complemented by X-ray, CT or magnetic resonance imaging (MRI) of hot spots. Before each treatment cycle, patients had a physical examination, complete blood cell count and biochemical profile. All positive imaging procedures had to be repeated every two cycles and at the end of treatment. Thereafter, patients were followed every 3 months until disease progression or death. Tumor responses were assessed according to WHO criteria for complete or partial response (CR or PR), stable disease (SD) and progressive disease (PD). All patients who completed at least the first two cycles of therapy were considered eligible for response to treatment evaluation. Time to disease progression (TTP) was calculated from the time of the first treatment infusion to the time of the first objective evidence of tumor progression. Overall survival (OS) was calculated from the first day of treatment to the date of last follow-up or documented death.

Drug administration:

Patients were randomized to receive either docetaxel 100mg/m^2 infused over 1 hour on day 1 of a 3-week cycle or a combination of VNB 25 mg/m^2 over a 30-min infusion, LV 30mg/m^2 administered by iv bolus injection, followed by 5-FU 600mg/m^2 as a continuous 24-h intravenous infusion on days 1 and 8 of each 21-day cycle.

Premedication with dexamethasone at a dose of 8mg twice a day for 3 days, starting the day before each docetaxel infusion. In both arms, treatment was planned for at least two cycles and assessment of response was performed every two cycles. Patients with CR, PR or SD continued the treatment protocol until a maximal tumor response, disease progression, unacceptable toxicity or patient refusal.

Toxic effects were graded using the National Cancer Institute common toxicity criteria. If patients experienced dose-limiting toxicities defined as grade 3 or a second occurrence of grade 2 non haematological toxicity, grade 3 neutropenia asso-
associated with fever >38.5°C, grade 4 neutropenia or ≥ grade 3 thrombocytopenia, treatment was withheld until the toxic effect resolved to ≤ grade 1 and was then reinstituted at a 20% dose reduction. A maximum of two dose reductions per patient were allowed for both docetaxel and 5-FU, and only one for VNB. Dose re-escalation was not allowed.

Statistical analysis:

The statistical analysis of data was done by using excel program and SPSS program (statistical package for social science) version 10. The description of the data was done in form of mean and median ± SD for quantitative data and frequency and proportion for qualitative data. The analysis of the data was done to test statistical significant difference between groups. For quantitative data, student t-test was used to compare between 2 groups. Chi-square test was used to compare qualitative data. Multivariate analysis was done using significant data in univariate analysis to detect the most predictable variable for TTP and OS. Correlation coefficient was done to detect association between variables.

N.B: P is significant if ≤0.05 at confidence interval 95%.

Results

Between December 2005 and June 2008, 60 patients with measurable MBC were enrolled in this study, with 31 patients were in the docetaxel arm and 29 patients were in the VLF arm. Both arms were well balanced (Table 1). The average age was 53.5 years (range from 31 to 67 years old). The performance status was grade 0-1 in 87% of patients in the docetaxel arm and 82.7% in the VLF arm. All patients were treated with anthracyclines as adjuvant chemotherapy. Eighty-three percent of patients in the docetaxel arm and 79% in the VLF arm had visceral metastases. The median number of organs involved was two. The majority of patients (53.5%) had liver metastases. A total of 196 cycles and 185 cycles were administered to the docetaxel and VLF arms, respectively. The median number of delivered cycles in all patients was 6 cycles (range, 2-9). Dose reductions secondary to treatment-related toxicity were made in 9 patients in each treatment arm.

There were three cases with CR (9.7%), 13 (41.9%) PR, 9 (29%) SD and 6 (19.4%) with PD in the docetaxel arm. There were two (6.9%) CR, 11 (37.9%) PR, 9 (31.1%) SD and 7 (24.1%) with PD in VLF arm. The overall response rate (ORR) for docetaxel and VLF arms was 51.6% and 44.8% respectively (p=0.6) (Table 2). The median duration of objective responses was 15 months (CI 95% 8.7-21.3) in the docetaxel arm and 14 months (CI 95% 10.9-17.1) in VLF arm (p=0.9). The ORR for patients with 1, 2 or >2 organs involved were 75, 53.8 and 30% respectively in the docetaxel arm; and 50, 50 and 36.4% respectively in VLF arm. These rates did not differ significantly between the two arms.

All patients were included in the survival analysis with 22.6% of patients in the docetaxel arm and 24.1% in VLF arm have experienced no disease progression. The median TTP was 9 months (CI 95% 7.01-11) in the docetaxel arm and 8.5 months (CI 95% 5.2-11.7) in VLF arm (p=0.6). The 1-year progression free survival for the docetaxel and VLF arm were 29% and 24% respectively (Fig. 1).

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<th>Table (1): Baseline characteristics of the patients treated in the study</th>
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Various factors were assessed to determine significant prognostic factors for TTP and OS in all patients. By univariate analysis performance status, number of metastatic sites, visceral metastases and type of response were significantly correlated with TTP ($p=0.007, 0.001, 0.003$ and $0.000$ respectively). In terms of OS, performance status, visceral metastases and type of response were the significant predictors ($p=0.007, 0.04$ and $0.000$ respectively). The multivariate stepwise analysis confirmed that non of the previously mentioned factors significantly affect OS while number of metastatic sites, visceral metastases and type of response were significant predictors for TTP ($p=0.008, 0.01$ and $0.03$ respectively).

Multivariate analysis of the above mentioned prognostic factors in each treatment group revealed that only number of metastatic sites and visceral metastases were significant predictors for TTP ($p=0.008$ and $0.01$ respectively).

The extent of toxicity experienced during the study is summarized in (Table 3). The most common serious toxicity was haematologic. Neutropenia was the main toxicity with an incidence of grade 3–4 in 19 patients (61%) in the docetaxel arm and 14 patients (48%) in VLF arm. Other haematological toxicities include grade 3 anemia in 3 patients in docetaxel arm and 2 patients in VLF arm; and grade 3 thrombocytopenia in only one patient in VLF arm.

Among nonhaematologic toxicities, gastrointestinal disorders were the most frequently reported. Nausea and vomiting were more frequent with VLF combination than with docetaxel (31% Vs 19% respectively), and grade 3 was reported...
in one patient in VLF arm. Grade 3 stomatitis and diarrhea occurred in 3.4% and 10% of patients received VLF combination Vs 3.2% for each in the docetaxel arm.

Peripheral neuropathy was mild and of low incidence in both arms. Total alopecia occurred more frequently with docetaxel than with VLF combination (80% Vs 55% respectively; \( p=0.03 \)). Grade 1/2 nail changes were reported in 19% of patients in the docetaxel arm Vs 14% in VLF arm. While docetaxel led to peripheral edema in 2 (6.5%) patients mild to moderate degree hand-foot syndrome characteristic side effect of 5-FU was reported in 4 (14%) patients in VLF arm.

Cycle delay and dose reduction occurred in 45% and 29% of patients in the docetaxel arm compared with 38% and 31% of patients in VLF arm respectively. Day 8 VLF administration was canceled in 5 patients (17%).

The majority of deaths in both treatment arms were due to progressive disease. No toxic death occurred during study treatment.

**Discussion**

While breast cancer is generally sensitive to initial treatment, resistance almost always develops in metastatic disease. The efficacy of treatment deteriorates rapidly with more lines of therapy. Efforts have therefore made to give first-line treatment that will maximize tumor response, but with acceptable toxicity.

Prior to the current standard treatment, single-agent docetaxel, several chemotherapy regimens were used after the failure of anthracycline based regimens. These included VNB plus 5-FU \([4,21]\). The current study was designed to compare the efficacy and safety of docetaxel with that of VLF combination. In terms of efficacy, there were no significant differences in TTP, response rate, response duration or OS between the two treatments however, there was a trend towards higher response rates, and longer TTP and OS with docetaxel though the difference was statistically not significant.

Our findings observed in both arms of the study were similar to those seen in other studies. A response rate of 51.6% (9.7% CR) for docetaxel reported in our study was similar to the response rate of 57% (10% complete responses) observed by Piccart in the metaanalysis of taxane-based combinations as first-line therapy of MBC patients \([22]\). The median TTP (9 months) and OS (18 months) for docetaxel in our trial were also consistent with those obtained by Piccart et al. \([22]\). Similar results were reported by Rispoli et al. \([23]\). Our results seemed to be at variance with those obtained by Jones et al. and Rivera et al. \([24,25]\) who reported lower response rates and shorter TTP. However, a large number of MBC patients in both trials received docetaxel as second-line therapy.

Bonnetere et al. \([26]\) compared docetaxel with 5-FU plus VNB in patients with MBC. In their study, there were no significant differences neither in response nor in survival between both arms. Interestingly, the ORR, TTP and survival were shorter in both arms than those observed in our study. This could be explained by high rate of anthracyclin resistance and palliative chemotherapy pretreated patients included in Bonnetere study. Similar poorer results were also demonstrated by Nabholtz et al. \([27]\) who compared docetaxel as a single agent against vinblastin and mitomycin C.

In our study, the ORR, TTP, OS for VLF arm were consistent with those obtained by Welt et al., Komek et al., Serin et al., Nole et al. and Burstein et al. \([13,28-31]\) whereas better ORR were reported by Yeh et al., Nole et al. and Blajman et al. \([21,32,33]\) that may be due to higher rate of chemo naive patients included in these studies.

The safety profiles of both docetaxel and VLF combination differed. Docetaxel induced higher incidence of neutropenia, alopecia, skin and nail disorders, whereas VLF combination was responsible for more thrombocytopenia and gastrointestinal disorders. The incidence of serious haematologic and nonhaematologic toxicities in patients receiving docetaxel in our study was consistent with those reported in the literature \([23,25-27,34]\). Less frequent haematologic and non haematologic toxicities were reported by both Lin et al. \([38]\) who used a relatively low dose docetaxel and Gamucci et al. \([36]\) who used docetaxel at weekly schedule.

For VLF patients in our study, the incidence of serious haematologic and non haematologic toxicities was similar to that reported in other studies \([13,28,32,37]\) but in variance with Stuart et al. and Yeh et al. \([4,21]\) who reported more frequent neutropenia and infection which may be due to high dose and prolonged infusion schedule of 5-fluorouracil as well as high incidence of alopecia and cardiac toxicity reported by Elomaa et al. \([37]\) because of the addition of epirubicin to this regimen.

In conclusion, this study revealed that both single agent docetaxel and VLF combination regimens were active for MBC after adjuvant anthra-
cyclines. There appeared to be a trend toward higher response rate and longer TTP and OS in favor of docetaxel with comparable toxicity profile for both regimens. Given the increasing use of docetaxel in adjuvant chemotherapy, regimens such as VLF will play an increasing part in the treatment of relapsed breast cancer which warrant future clinical trials on large number of patients and prolonged follow-up.

References

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