A Phase II Trial of Oral Vinorelbine and Capecitabine in Anthracycline Pretreated Patients with Metastatic Breast Cancer

JINDRICH FINEK1, LUBOS HOLUBEČ JR.1, TOMAS SVOBODA1, LUCIE SEFRHANSOVA1, IVANA PAVLIKOVÁ1, MARIE VOTAVOVA1, MARCELA SEDIVA2, STANISLAV FILIP3, RENATA KOZEVNIKOVA4 and STANISLAV KORMUNDA1

1University Hospital Pilsen; 2University Hospital Bulovka Prague; 3University Hospital Hradec Králové; 4DTC Centre in Prague, Czech Republic

Abstract. Background: Optimal chemotherapy (CT) for advanced breast treatment should be effective, well tolerated and convenient. In this study the efficacy and safety of the fully oral combination of oral vinorelbine (Navelbine Oral) plus capecitabine (Xeloda) in metastatic breast cancer (MBC) patients pretreated with anthracycline, was evaluated. Patients and Methods: In this phase II multicenter study, this combination CT was given as a first- or second-line therapy for MBC. The treatment schedule was: oral vinorelbine 60 mg/m2 day 1 and day 8 plus capecitabine 1,000 mg/m2 twice daily from day 1 to day 14, every 21 days. Results: One hundred and fifteen patients were included in this trial. The median age was 58 years (range: 40-75). All the patients had received prior anthracycline-based chemotherapy. The combination was well tolerated, with, in particular, only 0.8% of patients presenting with febrile neutropenia. In the intention-to-treat (ITT) population, an objective response was achieved in 65 patients (56.5%). A complete response was achieved in 22 patients (19.1%); partial response in 43 patients (37.4%); stable disease in 36 patients (31.3%), and progressive disease was observed in 14 patients (12.2%). After a median follow-up of 10.0 months, the median progression-free survival (PFS) was 10.5 months and the median survival was 17.5 months. Conclusion: Oral vinorelbine-capecitabine shows very promising activity and low toxicity in MBC treatment, with high compliance of the patients.

Metastatic breast cancer (MBC) is a highly heterogeneous disease where particular criteria must be considered, taking into account not only the clinical and biological parameters but also patient expectations and preferences. The objectives of an optimal chemotherapy (CT) for MBC are to prolong survival and to enhance the quality of life with minimal toxicity. The therapeutic strategy may include sequential single agents or combination CT (1, 2). In this setting, tolerability and acceptability are also of paramount importance for the compliance of patients.

In current practice, anthracycline-based regimens are given as a standard in the adjuvant setting. Due to the risk of cumulative cardiac toxicity of these agents, there is a need to develop non-anthracycline-containing alternatives in the metastatic relapse setting. Similarly, taxanes tend to be more and more used in the early-stage setting. Hence, their neurological and haematological toxicity profile even when albumin-bound nanoparticle agent is used, makes them a questionable option in certain patients at metastatic relapse.

At first relapse after anthracyclines and/or taxanes, treatment must meet two objectives: on one hand, to prolong survival and to obtain a response on the metastatic sites and symptoms; on the other hand, to be readily accepted by the patient. For challenging patients such as those who relapse with visceral metastases (lung, liver) after an anthracycline-based treatment (either in the adjuvant setting or in first-line metastatic disease), the combination of oral vinorelbine and capecitabine is one of the few anthracycline-free combinations possible and is the only all-oral combination. The rationale for this combination was provided by the wide experience with vinorelbine and fluoropyrimidine combinations (either 5-fluorouracil or capecitabine) in MBC, and by the preference expressed by patients for oral over intravenous treatments (3-7) which contributes to treatment acceptability.
This study assessed the efficacy and safety of the fully oral combination of vinorelbine (Navelbine Oral) plus capecitabine (Xeloda) in first- and second-line treatment of patients with MBC pretreated with anthracycline.

**Patients and Methods**

In this prospective, open, multicentre, phase II study, 115 patients were included between 2003 and 2006. This study took place in the Czech Republic, in the following oncology centres: the Faculty Hospital Pilsen, the Faculty Hospital Bulovka Prague, the Faculty Hospital Hradec Kralove and the the Diagnostic and Therapeutic Centre in Prague.

All patients gave their informed consent. The main inclusion criteria included: histologically confirmed invasive, Her2-negative breast cancer; at least one measurable lesion in extramammary tissue confirmed by X-ray, CT or MRI scan; age between 18 and 70 years; Karnofsky performance status ≥70% and failure of previous anthracycline-based chemotherapy in adjuvant and/or first-line treatment. The main exclusion criteria included previous treatment with adjuvant or palliative chemotherapy within 12 months prior to the study entry; concomitant hormonal therapy and radiation therapy of the only measurable lesion.

The treatment schedule was oral vinorelbine 60 mg/m² day 1 and day 8 and capecitabine 1,000 mg/m² twice daily from day 1 to day 14, every 21 days, until disease progression or unacceptable toxicity.

Statistical evaluation was performed by means of the statistical software CRAN 2.4.0. The basic statistical data, such as the mean, standard deviation, variance, median, inter-quartile range, minimum, and maximum were calculated for the continuous data. The categorical data were described by frequencies and percentages. The Kaplan-Meier method was applied to describe the time-dependent parameters (progression-free survival, PFS; overall survival, OS). The primary endpoint was the objective response (OR) evaluated according to the Response Evaluation Criteria in Solid Tumours (RECIST). The secondary endpoints were the PFS, OS, and the safety profile of the patients undergoing the oral CT.

**Results**

One hundred and fifteen women entered this study and all of them were evaluable for efficacy and toxicity. Table I details the patients’ characteristics. The enrolled patients had a median age of 58.5 years (range: 39.6-74.9). All had been previously treated with an anthracycline-based regimen, either as an adjuvant treatment (49.6%) or as first-line treatment after metastatic relapse (50.4%). The study treatment was therefore received as a first- or second-line
treatment in the metastatic setting respectively. A total of 801 cycles were administered (median: 6; range: 1-32). In 67.8% of the cases, the metastatic disease involved at least two sites. Liver and lung metastases were present in 31.3% and 25.2% of the patients respectively.

The efficacy results are detailed in Table II. Among the 115 evaluable patients, 65 (56.5%) had an OR. A response in the visceral metastases was achieved in 35 patients out of 62 (56.5%). With a median follow-up time of 10.0 months, the median PFS was 10.5 months and median OS was 17.5 months. At the cut-off date, 77 patients (67%) were still alive.

The safety profile of the combination of oral vinorelbine and capecitabine is detailed in Table III. The haematological toxicities were generally mild. Febrile neutropenia was observed in only one patient (0.8%), grade 3-4 thrombocytopenia and anaemia in 2.6% and 0.8% respectively. Although neutropenia is the most expected side-effect with vinorelbine, only 6 patients (5.2%) experienced a grade 3 or 4 neutropenia. The non-haematological toxicities were also generally mild. Grade 3 or 4 vomiting was experienced by 6.9% of the patients, but no prophylactic anti-emetic prophylaxis was given in this study. Grade 3 or 4 hand-foot syndrome was experienced by only 1.7% of the patients.

**Discussion**

This multicentre trial confirmed the efficacy and tolerance of this fully oral vinorelbine and capecitabine combination. A first-line response rate consistently greater than 50% has been observed with this combination in recent phase II studies, see Table IV (8-11). Beyond the overall response rate and OS observed in the present study, in line with standard treatments, this combination appeared particularly effective against life-threatening metastases, with a response rate of 56.5% on liver and lung metastases.

Moreover, the 10.5 month PFS observed was a period during which the patient benefited from all the advantages of a fully oral treatment, including the possibility of delaying the implantation of a central venous access device. Thus the PFS translated directly into a prolonged infusion-free survival. Being treated at home with fewer visits to hospital is another advantage of this fully oral treatment.

An excellent tolerance profile was observed with rare severe clinical toxicities, a low incidence of hand-foot syndrome and very good haematological tolerance. This tolerance profile made it possible to plan to increase the dose of oral vinorelbine to 80 mg/m², the level recommended for single agent use and in most combinations.

An international phase II trial on 55 patients with MBC evaluated the efficacy and tolerance of the combination of oral vinorelbine at a dose of 80 mg/m² on days 1 and 8 (after a first cycle at 60 mg/m² to test patient’s individual myelosensitivity) plus capecitabine 2,000 mg/m² (1,500 mg/m² in women aged 65 or more) from day 1 to day 14 until progression or unacceptable toxicity (4). The good clinical and haematological tolerance profile achieved enabled the delivery of the optimal dose vinorelbine to 91% of the patients and a median number of 7 cycles, resulting in outstanding efficacy. The response rate was 52% in the whole study population, 71% in previously untreated patients and 40% in the patients pretreated with anthracycline and taxane. The median survival had not been reached after a median follow-up of 33.5 months. At the optimal

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**Table IV. Review of data from medical literature.**

<table>
<thead>
<tr>
<th>Reference</th>
<th>Schedule</th>
<th>No. of patients</th>
<th>Line of treatment</th>
<th>OR</th>
<th>TTP (months)</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delcambre et al. (8)</td>
<td>NVBo 60 mg/m² d 1,8 CAP 2500/d 1-14 q3w</td>
<td>46</td>
<td>1st: 89%</td>
<td>61%</td>
<td>na</td>
<td>na</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2nd: 9%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lorusso et al. (9)</td>
<td>NVBo 60 mg/m² d 1,8 CAP 2000/d 2-7 &amp; 9-16 q3w</td>
<td>38</td>
<td>Post anthracycline/taxane</td>
<td>39.4%</td>
<td>4.5</td>
<td>10</td>
</tr>
<tr>
<td>Nol’e et al. (10)</td>
<td>NVBo 60 mg/m² d 1,8,15 CAP 2000/d 1-14 q3w</td>
<td>52</td>
<td>1st</td>
<td>55%</td>
<td>8.4 (PFS)</td>
<td>na</td>
</tr>
<tr>
<td>Tubiana-Mathieu et al. (11)</td>
<td>NVBo 80 mg/m² d 1,8 (after 1st cycle at 60 mg/m²) CAP 2000/d 1-14 q3w</td>
<td>55</td>
<td>1st</td>
<td>52%</td>
<td>8.4 (PFS)</td>
<td>na</td>
</tr>
</tbody>
</table>

NVBo: Vinorelbine; CAP: capecitabine; OR: objective response; TTP: time to progression; OS: overall survival; PFS: progression-free survival; na, not applicable.
dosage of capecitabine in combination (2,000 mg/m²/day from day 1 to day 14 every three weeks) determined by that trial, the incidence of side-effects, particularly that of hand-foot syndrome, remained within acceptable rates and was lower than that observed when capecitabine was used at the recommended dose of 2,500 mg/m²/day as a single agent or in combination with docetaxel. This safety profile allowed the patients to be treated for a much longer duration, until progression.

In summary, these results indicated that oral vinorelbine plus capecitabine is a valid option whenever a combination chemotherapy is considered for treatment of women with MBC. This regimen is characterized by high response rates after anthracyclines and taxanes, no visible or disabling toxicity, manageable haematological toxicity and infrequent and moderate alopecia. Among its many other advantages for patients, it might also decrease stress and reduce the time spent in hospital by giving them the possibility of being treated at home.

Following the presentation of these results, the Czech Cancer Society recommends this combination as a standard treatment of metastatic breast cancer (12).

Acknowledgements

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References