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ORIGINAL ARTICLE

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Oral vinorelbine alone or in combination with trastuzumab in advanced breast cancer: results from a pilot trial

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Abstract *Introduction*: We evaluated the efficacy of oral vinorelbine (OV) (Navelbine oral® Boeringer-Ingelheim Austria) in patients with advanced breast cancer as first-line therapy or after progressing under earlier line chemotherapies alone or in combination with trastuzumab (T). *Patients and methods*: Seventy-eight patients [median age: 63.5 years (y), range (r): 38–84 years] were included into this trial. Patients with her-2/*neu* positive tumours received a combination of OV and T. Treatment effect was evaluated every three cycles and treatment continued until progression. OV was administered in a dose of 60 mg/m^2 on day 1 and 8, q = 21 days, and no dose escalation to 80 mg/m^2 was performed. *Results*: We observed a complete response in 5.9% of patients, partial remission in 22.1%, stable disease (SD) > 6 months in 33.8%, SD < 6 months in 2.9%, and progression despite treatment in 35.3%, respectively. Time to progression was 6 months (range 1–23+). The main toxicities consisted of nausea/vomiting (N/V) and neutropenia. Grade IV neutropenia was found in 5 patients (6.4%), grade III in 6 patients (7.7%) and grade I and II in 11.5%. We did not find any grade IV N/V in our patients, however, grade III N/V was observed in 3.8%. No other grade III and IV toxicities were reported. *Conclusion*: OV appears to be effective in the treatment of advanced breast cancer at the dose and schedule chosen. It is well tolerated, effective, and the oral formulation is an advantage for the patients as well as for the nursing staff.

Keywords Advanced breast cancer · Oral vinorelbine · Palliative chemotherapy · Trastuzumab · Immunotherapy

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Introduction

While metastatic breast cancer remains an incurable disease, individualized, risk adapted, palliative treatment depending on tumour biology, symptoms and metastatic sites is available today.

In her2/*neu* positive tumours, combination of chemotherapy and trastuzumab (T) (Herceptin®) has shown higher effectiveness than chemotherapy alone [1–5]. T is a monoclonal humanized antibody targeting the epidermal growth factor receptor 2 (her2/*neu*). A benefit, however, can only be found in tumours with her2/*neu* 3+ over-expression or, in case of 2+ over-expression, in cells with her2/*neu* gene amplification analysed by FISH (fluorescence in situ hybridization) [6]. Paclitaxel plus T was the first combination regimen established [7]. While in vitro studies were able to demonstrate an additive anti-tumour effect of this combination, other substances (vinorelbine, docetaxel and cisplatin) showed a synergistic effect [8]. In vivo, it was possible to demonstrate, that intravenous vinorelbine plus T regimens are not only superior to paclitaxel containing regimens in terms of toxicity [9], but also in terms of response and survival [4, 8, 10, 11].

Vinorelbine (5′-noranhydrovinblastine) is a semi-synthetic anti-cancer drug belonging to the catheranthus alkaloid family. Its mechanism of action is only partially known, but it is regarded to be like vinblastine and vincristin an antimicrotubule agent, arresting cell division in mitosis [12]. Activity of vinorelbine has been known since the early 1990 s, with second-line response

rates of 17–36% and first-line response rates of 40–44% [13].

Oral vinorelbine (OV) is a new formulation of vinorelbine, which is used as intravenous chemotherapy in advanced breast cancer in a dose of 25 or 30 mg/m^2. Vinorelbine is generally regarded as an active therapy with minimal side effects [14, 15]. At usual doses, similar levels of variability of pharmacokinetics were observed between oral and intravenous routes [16], also the safety profile appears to be comparable [17]. As conventional vinorelbine at a dose of 25 mg/m^2 corresponds with 60 mg/m^2 of OV and our group found the best results both in tumour control and side effects with 25 mg, as reported by different other groups, we used the 60 mg dosage throughout the entire therapy and did not escalate the dose after the first cycle [9, 18].

The oral formulation is an advantage for our patients, for the number of venous punctuations and the frequency of hospital visits, even in the outpatient setting, can be reduced [19].

Methods

All data were collected at the Department of Internal Medicine I, Division of Oncology at the Medical University of Vienna, Vienna, Austria.

Patients

Seventy-eight patients treated with OV were available for this chart review and all are currently evaluable for toxicity and 68 for response. All patients were suffering from histologically confirmed advanced breast cancer. Criteria for inclusion were as follows: presence of at least one measurable lesion, Karnofsky performance score ≥70%, life expectancy of >3 months, adequate organ function as defined by WBC count ≥3,500/μl, platelet count ≥100,000/μl, hematocrit ≥30%,and serum bilirubin and creatinine ≤ 1.25× upper limit of the institution's normal range. For staging evaluations, CT-scan of the chest and the abdomen, mammography and gynaecologic examination were mandatory. Echocardiography data reported were available. Patients with controlled brain metastatic disease (after whole brain radiotherapy, neurosurgical resection and/or boost irradiation of one to three metastases) were also eligible.

According to their her2/*neu* status, patients either received a monotherapy with OV or a combination of OV and T. Her2/*neu* status was assessed using immunohistochemistry (HercepTest). Patients with 3+ tumours were regarded eligible for T treatment. In her2/*neu* 2+ positive tumours, a FISH was performed. When her2/*neu* gene amplification was found, tumours were again deemed eligible for T. Before initiation of T treatment, echocardiography was mandatory. Measurement of left ventricular ejection fraction was repeated at intervals of 3–6 months.

Treatment plan and patient evaluation

All treatment was administered in an outpatient setting. Vinorelbine was given orally at a dose of 60 mg/m^2 on day 1 and 8; this schedule was repeated in 3-week cycles, without dose escalation to 80 mg/m^2. Blood count was tested on day 1, 8, and 15 of the first cycles, during later cycles only on day 1. The combination therapy consisted of OV and T, administered in a dose of 8 mg/kg body weight loading dose on the first day of treatment, followed by 6 mg/kg body weight every 3 weeks [20].

Re-evaluation of patients' tumour status was performed with CT-scan of the chest and the abdomen with additional work up if indicated every three cycles of therapy according to WHO criteria. Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of 8 weeks. Partial response (PR) was defined as 25% or more reduction in the sum of the products of greatest diameters of measurable lesions, no increase of lesion size and no new lesions. Stable disease (SD) was defined as less than 25% decrease and less than 25% increase without the appearance of new lesions. Progressive disease (PD) was defined as greater than 25% increase in tumour size or the appearance of new lesions.

Statistical analysis

Time to progression (TTP) was defined as the interval from the first day of vinorelbine application until tumour progression. Data were analysed as of August 2004. TTP was estimated using the Kaplan–Meier product-limit method [21]. Toxicity was evaluated according to the WHO criteria and was recorded per patient as the worst episode that appeared during a cycle of treatment.

Results

Patient characteristics

Seventy-eight patients, median age 63.5 years (range 38–84 years) suffering from advanced breast cancer were included in this evaluation. Fifty-seven patients received OV as monotherapy; 21 were in the combination-therapy group.

Oral vinorelbine was used as first-line therapy in 39 patients (50%), second line in 26 patients (33.3%), third line in 10 patients (12.8%), fourth line in 2 patients (2.6%), and fifth line in 1 patient (1.3%). Table 1 lists the characteristics of the 78 patients included.

Out of all 78 patients, 4 (5.1%) started treatment, but were lost to follow-up with no evidence of PD or severe

Table 1 Patient characteristics

Characteristics	Patients
Entered	78
Karnofsky performance score	90–100%
Age (years)	
Median (range)	63.5 years (range 38–84 years)
Estrogens receptor/progesteron receptor positive	45/31
Adjuvant chemotherapy	41 (52.6%)
Adjuvant/palliative endocrine therapy	49 (62.8%)
Vinorelbine monotherapy group	57
First line	25
Second line	21
≥Third line	11
Combination therapy group	21
First line	15
Second line	4
≥Third line	2
Metastatic sites	
Lung	27
Liver	21
Bones	40
Lymph nodes	21
Soft tissue	23
Brain	2
Local	13
More than one metastatic site	49

toxicity on initial therapy. One patient (1.3%) discontinued therapy on her own wish due to nausea/vomiting (N/V) (WHO grade II) and was switched to IV vinorelbine. Therefore, these patients were not evaluable for response, but for toxicity.

Efficacy

Median time of observation (TOO) was 6 months, range 1–23+. TOO in the monotherapy group was 4 months (range 1–23+), and 6 months (1–15) in the combination group, respectively.

Sixty-eight patients are currently evaluable for response (51 monotherapy group and 17 combination group). Four patients showed a CR (5.9%), PR was observed in 15 patients (22.1%), SD > 6 months in 23 (33.8%), SD > 3/< 6 months in 2 (2.9%), and PD in 24 patients (35.3%), translating into an overall response rate of 28% and a clinical benefit rate (CBR) of 61.8% (Table 2). Median TTP was 6 months, range 1–23+, CI (95%) 5.31–6.69. Corresponding numbers for the monotherapy group were PR 10 (19.6%), SD > 6 months 17 (33.3%), SD > 3 months/< 6 months 2 (3.9%), PD 22 (43.1%), CBR 27 (52.9%) and for the combination group CR 4 (23.5%), PR 5 (29.4%), SD > 6 months 6 (35.3%), PD 2 (11.8%), overall response rate 52.9% and CBR 15 (88.2%), respectively. Median TTP was 6 months, range 1–23+, CI (95%) 4.86–7.14 in the monotherapy group and 10 months, range 3–15, CI (95%) 6.42–13.58, in the combination group (Fig. 1).

Subgroup analysis for patients receiving vinorelbine monotherapy as first-line or beyond first-line treatment revealed a CBR of 65.2 and 42.9%, respectively. Numbers for the combination-therapy group were 84.6% CBR in first-line treatment and 100% CBR beyond first line.

Toxicity

Both OV alone and the combination with T were well tolerated and all patients completed the therapy on an outpatient basis. Seventy-eight patients received a total of 458 cycles, 330 in the OV and 128 in the OV plus T group. Side effects appearing in both groups are shown together in Table 3, because of equal frequency and severity of toxicities in mono- and combination treatment. There were no treatment-related deaths. Notably, no case of congestive heart failure (CHF) was observed under T treatment. The main toxicities consisted of nausea and neutropenia.

Grade IV neutropenia was found in 5 patients (6.4%), grade III in 6 (7.7%), grade I and II combined in 9 (11.5%). We did not find any grade IV N/V, however, grade III N/V was observed in 3 (3.8%) of our patients. No other grade III and IV toxicities were reported. Other toxicities (grade I and II combined) included anaemia, thrombocytopenia, diarrhoea, and abdominal pain. Renal impairment or allergic reactions were not reported.

In 9 patients (11.5%), a delay of cycles was necessary because of neutropenia. Overall, 10/458 (2.2%) cycles had to be delayed. In 3 patients (3.8%), a dose reduction to 75% of initial dosage was necessary for severe neutropenia.

Echocardiography data are available from 52 patients (66.7%) with only 2 patients presenting with cardiac output rate of less than 50% (42 and 45.5%). Both patients were in the monotherapy group.

Discussion

The results presented here demonstrate that OV is an effective anti-tumour agent with a manageable toxicity profile at a dose of 60 mg/m^2 without dose escalation. In fact it is better tolerated than most other cytotoxic agents available in metastatic breast cancer.

Oral vinorelbine produced a response rate of 28% and SD in 33.8%, resulting in a CBR of 61.8%. As we expected, results for first and beyond first-line treatment were superior for the vinorelbine plus T group, underlining the synergistic anti-tumour effect known from

Table 2 Response rates (n = 68 patients)

Group	Response						
	CR	PR	ORR	SD ≥ 6 months	CBR	SD > 3 months/< 6 months	PD
Response overall (n = 68)	4 (5.9%)	15 (22.1%)	19 (28%)	23 (33.8%)	42 (61.8%)	2 (2.9%)	24 (35.3%)
Response vinorelbine (n = 51)		10 (19.6%)	10 (19.6%)	17 (33.3%)	27 (52.9%)	2 (3.9%)	22 (43.1%)
First line (n = 23)		6 (26.1%)	6 (26.1%)	9 (39.1%)	15 (65.2%)		8 (34.7%)
Beyond first line (n = 28)		4 (14.3%)	4 (14.3%)	8 (28.6%)	12 (42.9%)	2 (7.1%)	14 (50%)
Response combination (n = 17)	4 (23.5%)	5 (29.4%)	9 (52.9%)	6 (35.3%)	15 (88.2%)		2 (11.8%)
First line (n = 13)	3 (23.8%)	4 (30.8%)	7 (54.6%)	4 (30.8%)	11 (84.6%)		2 (15.4%)
Beyond first line (n = 4)	1 (25%)	1 (25%)	2 (50%)	2 (50%)	4 (100%)		

CR, complete remission; PR, partial remission; ORR, overall response rate (CR + PR); SD ≥ 6 months, stable disease for at least 6 months; SD > 3 months/< 6 months, stable disease for more than 3 months, but less than 6 months; CBR, clinical benefit rate (CR + PR + SD≥6 months); PD, progressive disease

intravenous vinorelbine. Therefore, the combination with the monoclonal antibody can be recommended to early use during the course of palliative treatment in her2/*neu* positive patients [6]. The combination produced encouraging results in the first-line setting as well as beyond first line, albeit the CBR of 100% in the beyond first-line group is of course overoptimistic and results from the small patient number in this subgroup.

In patients with her2/*neu* negative tumours, the situation must be analysed more carefully. While vinorelbine monotherapy is among the least toxic options available, it produces lower response rates in comparison to docetaxel and capecitabine, both combined and alone [22]. In patients with low-risk metastatic disease, who are not eligible for endocrine therapy, and also in patients not willing to accept an increased toxicity, OV as first-line therapy might be a feasible option. Still, the important role of vinorelbine in the treatment beyond first line is underlined by our results.

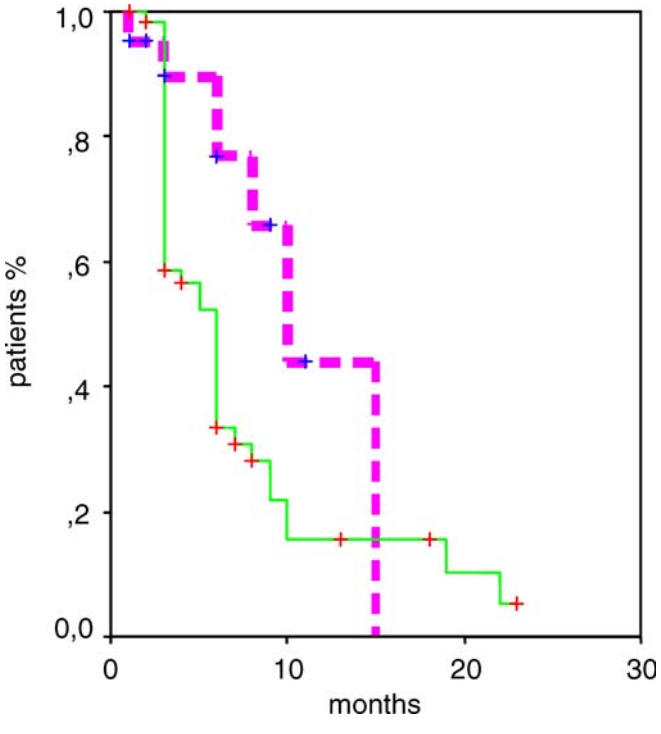

Fig. 1 Time to progression

The only major difference in toxicity between OV and conventional vinorelbine was a higher incidence in N/V, a fact also reported by various other groups. This side effect, however, was easily manageable with prophylactic use of proton-pump-inhibitors and 5-HT3 antagonists. Only 1 patient opted to discontinue oral treatment in favour of intravenous therapy because of nausea, but even this patient showed a maximum of grade II nausea according to CTC criteria only. Nausea decreased to grade I after this switch.

Our toxicity rates are considerably lower than those reported by groups using either standard 80 mg/m^2 of oral [23, 24] or 30 mg/m^2 of intravenous vinorelbine [6]. Freyer et al. and Trillet-Lenoir et al. reported haematologic toxicity rates of 39–42% grade III and IV neutropenia and 6.3% anaemia, while in our patients, grade III and IV neutropenia were observed in only 14.1%. No case of grade III and IV anaemia was to be found. Those trials, together with our own experience with intravenous vinorelbine at a dose of 30 mg/m^2 as well as with 80 mg/m^2 of OV, convinced us that a gain in overall response would be paid for with huge excess toxicity. Further, it must be questioned whether a high overall response rate is more important than a high CBR in metastatic patients. As it is not always possible to compare efficacy data from different phase II trials, it must be stated that while our regimen of 60 mg/m^2, day 1 and 8, q21 appears equieffective, randomized prospective trials are necessary in the future. Furthermore, our results are both limited by the imbalance in patient numbers in the mono- and combination-therapy group, and by the relatively small number of patients in

Table 3 Toxicities (n = 78 patients)

Toxicity	WHO grade			
Nausea/Vomiting	I	II	III	IV
Without prophylaxis	12 (15.4%)	14 (17.9%)	3 (3.8%)	–
With secondary prophylaxis[a]	8 (10.3%)	2 (2.6%)	1 (1.3%)	–
Neutropenia	4(5.1%)	5(6.4%)	6 (7.7%)	5(6.4%)
Thrombocytopenia	2(2.6%)	–	–	–
Anaemia	12(15.4%)	2(2.6%)	–	–
Diarrhoea	2(2.6%)	3(3.8%)	–	–
Stomatitis	–	1(1.3%)	–	–
Alopecia	1(1.3%)	–	–	–
Polyneuropathia	1(1.3%)	–	–	–
Abdominal Pain	1(1.3%)	1(1.3%)	–	–

[a]Prophylaxis with 5-HT3 antagonists (tropisetron 5 mg) on days 1 and 8

the subgroup analysis. Further, with her2/*neu* positive and negative tumours, we included two biologically different subtypes of breast cancer [25–28].

We conclude that OV is active and relatively well tolerated in patients with advanced breast cancer at the dose and schedule chosen. The new oral formulation is a step forward in the quality of life of our patients. Our 60 mg/m^2 regimen without dose escalation has proven to produce a lower rate of toxicity in comparison to standard treatment. Still, in terms of noninferiority, randomized, prospective trials with more patients accrued are warranted.

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