

Clinical Study

Final Safety and Efficacy Analysis of a Phase I/II Trial with Imatinib and Vinorelbine for Patients with Metastatic Breast Cancer

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Key Words

Phase I/II trial · Metastatic breast cancer · Imatinib mesylate · Vinorelbine · KIT · PDGFR- α and - β

Abstract

Background: Imatinib is a tyrosine kinase inhibitor of BCR-ABL, ABL, PDGFR- α and - β , KIT, and DDR. In solid tumors, it inhibits proliferation and invasiveness and facilitates higher intratumoral cytotoxic drug concentrations. Vinorelbine has good tolerability and efficacy in metastatic breast cancer (MBC). This study evaluates the safety and efficacy of imatinib and vinorelbine in combination. **Methods:** In a prospective, open-label, phase I/II trial, 400 mg imatinib p.o. daily (corrected from 600 mg) was combined with an escalating dose of vinorelbine i.v. weekly in four dose levels of 10, 15, 20, and 25 mg/m² (each n \geq 5) to treat patients with MBC (expressing PDGFR- α and/or - β , and/or KIT). The last patient of each level was treated for >28 days, before enrolment for the next dose level started. Study endpoints were feasibility and tolerability, incidence of hematological and nonhematological toxicity, and clinical efficacy (data cutoff: November 18, 2011). A total of 33 patients have been enrolled, and all dose levels have been fully recruited. One patient is still on study medication. A translational subprotocol is ongoing. **Results:** All 33 included patients are evaluable for safety (32 within the ITT population). Eleven patients were excluded early from the study (progressive disease, toxicity, and withdrawal of consent). Twenty-two patients participated in the study for >28 days ('ITT >28'). Within the ITT population, the response rate [complete response (CR) and partial response (PR)] was 9.4% (n = 3), the clinical benefit rate (CBR; CR+PR+stable disease) 50% (n = 16), and the median time to progression (TTP) 155 days. A total of 21.3% of the patients were

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on study medication for >6 months, and 15.2% for >12 months (mean 140 days, range 15–643). Within 'ITT >28', the response rate was 13.6%, CBR 72.7%, and median TTP 176 days. The response was independent of the receptor status (PDGFR- α , - β , and KIT). Toxicities were as follows (safety population): 21.6% severe leukopenia, 9.1% severe neutropenia (with 1 febrile neutropenia), 1 case of bowel perforation, 36% diarrhea (3% severe), 84.8% nausea (severe 15.2%), 48.5% vomiting (severe 9.1%), 27.3% infections (severe 6.1%), 12.1% peripheral neuropathy (severe 9.1%), and 36.4% dyspnea (3% severe). Four patients on trial died (nondrug-related). **Conclusion:** The combination of imatinib and vinorelbine in MBC appeared to be feasible and tolerable. A CBR of 50% (ITT) in pretreated patients suggests that this combination may be active. Although toxicities were frequent, they appeared to be manageable.

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Introduction

Imatinib (Gleevec®; Novartis Pharmaceuticals) is a tyrosine kinase inhibitor and was originally developed for targeted inhibition of the Philadelphia chromosome-related oncoprotein BCR-ABL in chronic myeloid leukemia [1, 2]. Imatinib is also able to inhibit receptor tyrosine kinases such as KIT, PDGFR- α and - β , DDR-1, and -2, which are important receptors in solid cancers [3]. These receptor tyrosine kinases have physiological functions in regulation of cell proliferation and differentiation, modulation of cellular metabolism, and promotion of cell survival. KIT aberrations are pathognomonic in gastrointestinal stroma tumors and are also found in different solid tumors as breast cancer [3–10]. PDGFR- α and - β activation occurs via an autocrine pathway or by paracrine effects of ligands. Inhibition of both subtypes leads to apoptosis. Coexpression of PDGFR- β and stimulating ligands can be seen in breast cancer and other solid malignancies. Increased stromal expression of PDGF receptors correlates with high-grade estrogen receptor negativity and HER-2/neu positivity. Especially PDGFR- β expression correlates with shorter recurrence-free and overall survival and an increased risk of distant metastasis as well as with decreased chemotherapy sensitivity [11–14]. Our previous data show an antiproliferative and proapoptotic effect of imatinib in breast cancer cell lines mainly mediated by inhibition of PDGFR- β and akt. Minor effects of KIT and PDGFR- α inhibition cannot be ruled out [9, 15]. Mediated by inhibition of PDGFR- β , imatinib leads to a decrease in interstitial fluid pressure of solid tumors, which leads to increased tumor oxygenation, helps to promote an intracellular uptake of cytotoxic agents, and improve sensitivity of cancer cells to cytostatic drugs [16]. Imatinib as a single agent has only minor inhibitory effects on breast cancer cells and no significant effects in early phase clinical trials of metastasized breast cancer [15, 17]. As tumor biology in solid tumors is driven by multiple factors, a combination of established cytotoxic agents and novel targeted drugs appears to be reasonable [18]. In advanced breast cancers, effective new combinations with limited toxicity are awaited. Imatinib is showing an enhanced radio- and chemosensitivity mediated by inhibition of PDGFR- β [19, 20].

In different phase II clinical trials, imatinib has been tested in combinations with paclitaxel, docetaxel, and capecitabine. The combination of paclitaxel and imatinib showed an overall response rate (RR) of 13.2% and an overall clinical benefit rate (CBR) of 47.4% [20]. Docetaxel and imatinib yielded an RR of 16% and a CBR of 26% [21]. Imatinib and capecitabine resulted in an RR of 11% and a CBR of 53% [22]. The combinations were moderately tolerated with common grade 3 toxicities as neutropenia, fatigue, diarrhea, and palmar-plantar erythrodysesthesia.

Vinorelbine has good tolerability and efficacy in metastatic breast cancer (MBC) as a single agent. After previous taxane and anthracycline therapies in the metastatic setting, it has produced varying results with RRs from 25 to 46% and a time to progression (TTP) of up

to 3 months. In numerous clinical trials, it has also served as a well-tolerated combination partner for other agents. Therefore, it was chosen as a combination partner for imatinib. Since a lower vinorelbine concentration led to the same inhibition of cell growth in combination with imatinib, we assume that a combination with imatinib may reduce unwanted side effects of chemotherapy [11, 12, 23–28].

In this open-label, single arm, phase I dose-escalating study (study ID CSTI571 #BDE28, ClinicalTrials.gov Identifier: NCT 00372476), the feasibility and efficacy of this drug combination is investigated for the first time clinically. The study combines imatinib mesylate with vinorelbine weekly for patients with locally advanced or metastasized breast cancer.

Material and Methods

Patient Eligibility

Eligible patients were aged ≥ 18 years and had measurable HER-2-/neu-negative MBC. Patients must have progressed on ≥ 1 previous regimen for metastatic disease and must have had a previous anthracycline-containing chemotherapy. In addition, the tumor must have an immunohistochemical (IHC) documentation of c-kit and/or PDGFR expression and must be evaluable (as defined by Southwestern Oncology Group Solid Tumor Response Criteria). Prior therapy with vinorelbine or imatinib was not allowed. All patients had to have a performance status of 0, 1 or 2 (ECOG) and adequate hematologic, cardiac, renal, and hepatic function as indicated by an absolute neutrophil count $>1,500$ cells/ μl , platelets $>100,000$ k/ mm^3 , creatinine clearance >60 ml/min, bilirubin within normal institutional limits, and aspartate aminotransferase as well as alanine aminotransferase <2.5 times the normal institutional limit. Patients were excluded if they had brain or CNS metastases, were pregnant, were HIV positive, had another invasive cancer within 5 years or any previous cancer not in remission or severe and/or uncontrolled medical disease (i.e., uncontrolled diabetes, chronic renal disease, or active uncontrolled infection).

The study has been performed in accordance with the local review board (ethics committee). All patients were informed of the investigational nature of the study and gave written informed consent.

Study Endpoints

In this phase I/II clinical trial, the primary objectives under evaluation were safety and tolerability (total toxicity, incidence of hematological toxicity/grade 3 and 4 and of nonhematological toxicity/grade 3 and 4) of this novel drug combination. Toxicities were classified using the Common Toxicity Criteria (CTC) grade (CTCAE Version 3.0). Secondary endpoints were clinical activity of the combination, such as clinical RR and TTP [27], using the SWOG response criteria. Patients with missing tumor response or who died or discontinued the study before having the first post-baseline assessment were considered to be nonresponders. In addition, quality of life (according to the EORTC QLQ-C30 and BR23 questionnaires) was measured at specific time points during the course of treatment. Before study admission, tumors had to proof expression of either c-kit and/or PDGFR by IHC stain of paraffin-embedded tumor tissue from a primary diagnosis or metastasis.

Study Treatment

A treatment cycle consisted of 400 mg imatinib p.o. daily on days 1–28. The imatinib dose was lowered from 600 mg to 400 mg daily because of toxicity (primarily nausea and other gastrointestinal disturbances) observed in the first 6 patients. Additionally a vinorelbine dose escalation was performed in four levels. Patients received i.v. cycles of vinorelbine at 10 mg/ m^2 (level 1), 15 mg/ m^2 (level 2), 20 mg/ m^2 (level 3) or 25 mg/ m^2 (level 4) weekly on days 1–28. During the first cycle, vinorelbine was given on days 8–28. In 5 patients, the levels were reached one after the other. Patients were assigned to one dose level and were exclusively treated within this dose level. Recruitment started for the lowest vinorelbine dose level. When the dose levels were all filled and no limiting toxicities occurred (in ≤ 1 of 5 patients) for at least 28 days, recruitment for the next higher dose level started. When patients withdrew their consent or were not evaluable for at least 28 days on treatment, they were excluded from the study and an additional patient was recruited for this dose level. In case of severe side effects or progressive disease (PD), patients were also excluded from the study. In case of remission or stable disease (SD), patients continued treatment.

The first patient visit occurred in June 2006, and 33 patients from one center were enrolled and treated in this study. The last patient completed the trial in July 2012.

Table 1. Overall exposure in the safety population

Imatinib/ vinorelbine	Overall exposure					Total (n = 33)
	600 mg/ 10 mg/m ² (n = 6)	400 mg/ 10 mg/m ² (n = 5)	400 mg/ 15 mg/m ² (n = 10)	400 mg/ 20 mg/m ² (n = 6)	400 mg/ 25 mg/m ² (n = 6)	
Duration category in days, n (%) ^a						
1–28	3 (50.0)	0	3 (30.0)	2 (33.3)	0	8 (24.2)
29–84	1 (16.7)	3 (60.0)	2 (20.0)	2 (33.3)	2 (33.3)	10 (30.3)
85–182	1 (16.7)	0	3 (30.0)	2 (33.3)	2 (33.3)	8 (24.2)
183–365	0	0	2 (20.0)	0	0	2 (6.1)
>365	1 (16.7)	2 (40.0)	0	0	2 (33.3)	5 (15.2)
Duration in days ^a						
Mean ± SD	109±178	209±216	95±79	66±47	261±289	140±177
Median	32	63	83	60	115	63
Range	15–468	44–484	15–204	22–147	29–643	15–643
Average daily dose of vinorelbine ^b						
Mean ± SD	2.4±0.5	2.4±0.3	3.7±0.4	4.1±0.6	4.3±0.6	3.4±0.9
Median	2.5	2.4	3.8	3.9	4.3	3.7
Range	1.9–3.1	2.0–2.9	2.8–4.1	3.5–5.0	3.3–5.0	1.9–5.0

Eight patients discontinued trial medication early (<28 days). One patient was still on trial at the date of the data cutoff. At least one change of the imatinib dose was reported in 42.4% of the patients (most frequent reason: dose after recovery) and at least one change of the vinorelbine dose was reported in 78.8% of the patients (most frequent reason: hematological toxicity NCI CTC grades 3–4). One patient at the 400 mg/15 mg/m² dose level received only imatinib.

^a Imatinib + vinorelbine; ^b vinorelbine was administered weekly.

IHC Detection of KIT and PDGFR-α and -β

Tumor sections were deparaffinized in xylene and rehydrated with graded alcohols. Epitope retrieval was performed before application of primary antibodies. Slides were incubated at room temperature. For staining of KIT, PDGFR-α and -β primary antibody incubation was 40 min followed by Envision+ labeled polymer for 30 min and DAB+ substrate for 5 min (Dako). Sections were counterstained with hematoxylin. Results of all antibodies were scored in a semiquantitative fashion (0, 1+, 2+, 3+) on the basis of the percentage of positive cells.

Statistical Methods

Analysis populations were defined as follows: The safety population included all patients who received at least one dose of imatinib or vinorelbine. The ITT (intent-to-treat) population included all enrolled patients who received at least one dose of imatinib and vinorelbine. The population analyzable for efficacy consisted of all patients who received the study drug combination for at least 3 weeks. Efficacy evaluation: best overall response. The crude RR was calculated based on the investigator's assessment. A Kaplan-Meier estimator together with the corresponding 95% confidence interval (CI) was additionally presented. TTP was presented as Kaplan-Meier curve and median TTP was planned to be compared against historical controls.

Results

All 33 patients included in this trial were evaluable for safety. A total of 32 patients were part of the ITT population. Five different dose levels have been assigned to the patients. Ten patients were older than 65 years, with a mean age of 60.2 years (42–71). All, but 1 patient were postmenopausal. Eleven patients were excluded early from the study (PD, toxicity, and withdrawal of consent). Twenty-two (67%) patients participated in the study for >28 days

Table 2. Presentation of the most frequent AEs^a in the safety population

Imatinib/vinorelbine	Most frequent AEs					Total
	600 mg/ 10 mg/m ²	400 mg/ 10 mg/m ²	400 mg/ 15 mg/m ²	400 mg/ 20 mg/m ²	400 mg/ 25 mg/m ²	
Total number of patients	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Total number of patients with AEs	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Total number of AEs	52	58	112	62	243	527
AE preferred term						
Nausea	6 (100.0)	4 (80.0)	9 (90.0)	5 (83.3)	5 (83.3)	29 (87.9)
Fatigue	2 (33.3)	4 (80.0)	7 (70.0)	2 (33.3)	5 (83.3)	20 (60.6)
Vomiting	3 (50.0)	2 (40.0)	5 (50.0)	3 (50.0)	3 (50.0)	16 (48.5)
Diarrhea	3 (50.0)	2 (40.0)	3 (30.0)	2 (33.3)	2 (33.3)	12 (36.4)
Dyspnea	1 (16.7)	2 (40.0)	5 (50.0)	1 (16.7)	3 (50.0)	12 (36.4)
Hemoglobin decreased	0	1 (20.0)	3 (30.0)	2 (33.3)	3 (50.0)	9 (27.3)
Leukopenia	0	0	2 (20.0)	3 (50.0)	4 (66.7)	9 (27.3)
Pain in extremity	0	2 (40.0)	4 (40.0)	1 (16.7)	2 (33.3)	9 (27.3)
Abdominal pain	0	1 (20.0)	1 (10.0)	2 (33.3)	3 (50.0)	7 (21.2)
Decreased appetite	1 (16.7)	0 (0.0)	2 (20.0)	1 (16.7)	2 (33.3)	6 (18.2)
Pleural effusion	2 (33.3)	2 (40.0)	1 (10.0)	1 (16.7)	0	6 (18.2)
Pyrexia	1 (16.7)	2 (40.0)	1 (10.0)	1 (16.7)	1 (16.7)	6 (18.2)
AST increased	0	0	2 (20.0)	1 (16.7)	2 (33.3)	5 (15.2)
Blood LDH increased	1 (16.7)	0	2 (20.0)	1 (16.7)	1 (16.7)	5 (15.2)
Bone pain	0	0	2 (20.0)	2 (33.3)	1 (16.7)	5 (15.2)
Cough	0	0	2 (20.0)	1 (16.7)	2 (33.3)	5 (15.2)

Values are n (%). All patients in the safety population experienced at least one AE. The total number of AEs was highest at the 400 mg/25 mg/m² dose level. Sort order is by decreasing incidence in the total group. AST = Aspartate aminotransferase; LDH = lactate dehydrogenase.

^a >15% in the total group.

('ITT >28') and were analyzable for efficacy. Of the 6 patients who were treated at level 1 with 600 mg/10 mg/m² as originally planned, 5 discontinued the treatment due to adverse events (AEs; 1 patient on day 15 and 1 on day 17), and 1 patient withdrew her consent. In order to improve the tolerability of the study treatment, it was decided to reduce the imatinib dose to 400 mg (amendment 2; issued on May 10, 2007). With this reduction, dose escalation starting with vinorelbine 10 mg/m² weekly could be performed at the 100% level of 400 mg/25 mg/m². One of the 6 patients treated at this dose level was still receiving study treatment at the time of the data cutoff in July 2012. The mean BMI was 25.5 (17.0–33.1), and the mean body surface area was 1.8 m² (table 1).

Tumor History and Current Status of Disease

Between the first diagnosis of breast cancer and inclusion in this study, a median of >5 years (mean 63.7 months, range 3–235) had passed. The most frequent tumor types were invasive ductal carcinoma (72.7%) and invasive lobular carcinoma (9.1%). At primary diagnosis, 69.7% of the tumors were estrogen receptor-positive and 57.6% progesterone receptor-positive. All tumors were HER-2-/neu-negative. All patients received systemic antineoplastic pretreatment. Substances used included cyclophosphamide (81.8%), paclitaxel (63.6%), epirubicin (60.6%), and tamoxifen (54.5%). At study baseline, all 33 patients had locally advanced (21.2%) or/and MBC (100%). Before study entry, they had predominantly received

Table 3. Deaths and other serious or clinically significant AEs in the safety population

AEs, dose modifications, interruptions, and discontinuation	Imatinib/vinorelbine					Total
	600 mg/ 10 mg/m ²	400 mg/ 10 mg/m ²	400 mg/ 15 mg/m ²	400 mg/ 20 mg/m ²	400 mg/ 25 mg/m ²	
Total number of patients	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Number of patients with AEs	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
AEs requiring dose adjustment or study drug interruption	1 (16.7)	1 (20.0)	4 (40.0)	5 (83.3)	6 (100.0)	17 (51.5)
AEs causing study drug discontinuation	5 (83.3)	1 (20.0)	2 (20.0)	0 (0.0)	2 (33.3)	10 (30.3)
AEs requiring significant additional therapy	6 (100.0)	4 (80.0)	9 (90.0)	6 (100.0)	6 (100.0)	31 (93.9)
AEs related to imatinib	6 (100.0)	3 (60.0)	10 (100.0)	4 (66.7)	5 (83.3)	28 (84.8)
AEs related to vinorelbine	0	3 (60.0)	3 (30.0)	2 (33.3)	4 (66.7)	12 (36.4)
AEs related to comb. imatinib/vinorelbine	2 (33.3)	3 (60.0)	7 (70.0)	2 (33.3)	4 (66.7)	18 (54.5)
SAEs	4 (66.7)	3 (60.0)	5 (50.0)	2 (33.3)	2 (33.3)	16 (48.5)
SAEs causing study drug discontinuation	2 (33.3)	1 (20.0)	1 (10.0)	0	1 (16.7)	5 (15.2)
SAEs related to any study drug	3 (50.0) ^a	0	0	0	0	3 (9.1)
Deaths	0	2 (40.0)	2 (20.0)	0	0	4 (12.1)

Values are n (%). The incidence of AEs requiring dose adjustment (one event at 400 mg/10 mg/m² vs. 59 events at 400 mg/25 mg/m²) augmented with increasing vinorelbine dose. Of the 59 events in the 400 mg/25 mg/m² dose group, 43 events were blood and lymphatic system disorders and 12 events were gastrointestinal disorders.

AEs causing study drug discontinuation were most frequent at the 600 mg/10 mg/m² dose level, whilst their incidence showed no clear dose-dependent increase in the 400 mg imatinib + vinorelbine regimens. AEs causing study drug discontinuation, which were suspected to be related to imatinib, were one event of vomiting at the 600 mg/10 mg/m² dose level, one event of nausea, and one event of vomiting at the 400 mg/25 mg/m² dose level. One AE causing study drug discontinuation – polyneuropathy at the 400 mg/15 mg/m² dose level – was suspected to be related to vinorelbine. One AE causing study drug discontinuation – palmar-plantar erythrodysesthesia syndrome at the 600 mg/10 mg/m² dose level – was suspected to be related to the combination of imatinib and vinorelbine.

AEs with suspected relationship to imatinib were predominantly gastrointestinal disorders, which occurred in all patients at

the 600 mg/10 mg/m² dose level and in similar proportions of patients at the other dose levels. AEs with suspected relationship to vinorelbine were most commonly nervous system disorders and blood and lymphatic system disorders, the latter occurring almost exclusively at the 400 mg/25 mg/m² dose level. AEs with suspected relationship to the imatinib/vinorelbine combination were most commonly general disorders and administration site conditions such as fatigue with no clear trend when comparing the different dose levels.

SAEs occurred most frequently at the 600 mg/10 mg/m² dose level; in the 400 mg imatinib + vinorelbine regimens the SAE incidence showed no dose-dependent increase. A total of 9 SAEs in 3 patients (all at the 600 mg/10 mg/m² dose level) were suspected to be related to imatinib (nausea in patient No. 1, nausea and anemia in patient No. 3, and vomiting, diarrhea, nausea, and fatigue in patient No. 4). Except for nausea in patient No. 3, which was mild, all other events were of severe intensity. None of the reported SAEs were suspected to be related to vinorelbine or the imatinib/vinorelbine combination.

^a All cases were suspected to be related to imatinib.

several lines of therapies for MBC (median: 2.5, range 0–5). C-kit expression in primary tumors was positive in 35.7%, PDGF-R- α was positive in 89.3%, and PDGFR- β was positive in 10.7%.

Toxicities

All treated patients were included in the safety population. At study entry, 60% had a normal ECOG performance status (0), and 40% of the patients had ECOG performance status 1. In the ITT population, a variety of toxicities occurred: 21.6% of the patients suffered from severe leukopenia, 9.1% from severe neutropenia (with 1 case of febrile neutropenia), and 1 case of bowel perforation was observed. A total of 36% of the patients suffered from diarrhea (3% severe), 84.8% from nausea (severe 15.2%), and 48.5% from vomiting (severe 9.1%). Infections were observed in 27.3% of the cases (severe 6.1%), a peripheral neuropathy in 12.1% (severe 9.1%), and dyspnea in 36.4% of the cases (3% severe; table 2).

Table 4. Incidences of AEs by maximum severity in the safety population

AEs by maximum severity	Imatinib/vinorelbine					Total
	600 mg/ 10 mg/m ²	400 mg/ 10 mg/m ²	400 mg/ 15 mg/m ²	400 mg/ 20 mg/m ²	400 mg/ 25 mg/m ²	
Total number of patients	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
Total number of patients with AEs	6 (100.0)	5 (100.0)	10 (100.0)	6 (100.0)	6 (100.0)	33 (100.0)
AEs of moderate intensity	0 (0.0)	1 (20.0)	4 (40.0)	1 (16.7)	0 (0.0)	6 (18.2)
AEs of severe intensity	4 (66.7)	2 (40.0)	4 (40.0)	4 (66.7)	6 (100.0)	20 (60.6)
Life-threatening AEs	2 (33.3)	0 (0.0)	0 (0.0)	1 (16.7)	0 (0.0)	3 (9.1)
Death related to AEs	0 (0.0)	2 (40.0)	2 (20.0)	0 (0.0)	0 (0.0)	4 (12.1)

Values are n (%). Patients at the higher vinorelbine dose levels were more likely to suffer severe AEs. At the 400 mg/25 mg/m² dose level, these were predominantly blood and lymphatic system disorders. None of the life-threatening AEs were suspected to be related to study treatment.

Table 5. Efficacy results of the analyzable population

Efficacy results	Imatinib/vinorelbine					Total (n = 22)
	600 mg/ 10 mg/m ² (n = 3)	400 mg/ 10 mg/m ² (n = 5)	400 mg/ 15 mg/m ² (n = 5)	400 mg/ 20 mg/m ² (n = 4)	400 mg/ 25 mg/m ² (n = 5)	
Response ^a (CR or PR)	1 (33.3)	1 (20)	1 (20.0)	0	0	3 (13.6)
Clinical benefit (CR, PR or SD)	2 (66.7)	2 (40.0)	5 (100)	2 (50)	5 (100)	16 (72.7)

Values are n (%). The evaluation of efficacy was a secondary objective in this study. Results of best overall response according to the investigators assessment are summarized in this table. Median TTP was 176 days (95% CI 50–611) in the efficacy analyzable population. Due to the low sample sizes, comparison of the different dose levels was not conclusive. The evaluation of efficacy was a secondary objective in this study.

^a Best overall response according to the investigators assessment.

All patients in the safety population experienced at least one AE. The incidence of AEs (grades 3 and 4 toxicities) requiring dose adjustment or study drug interruption and also the absolute number of such events augmented with increasing vinorelbine dose (one event at 400 mg/10 mg/m² vs. 59 events at 400 mg/25 mg/m²). Of the 59 events in the 400 mg/25 mg/m² dose group, 43 events were blood and lymphatic system disorders, and 12 events were gastrointestinal disorders. AEs causing study drug discontinuation were most frequent at the 600 mg/10 mg/m² dose level, whilst their incidence showed no clear dose-dependent increase in the 400 mg imatinib + vinorelbine regimens (table 3). Four patients on trial died (unrelated to study treatment; table 4).

Efficacy

Within the ITT population, the RR [complete response (CR) and partial response (PR)] was 9.4% (n = 3), the CBR (CR+PR+SD) was 50% (n = 16), and the median TTP was 155 days. A total of 21.3% of the patients were on study medication for >6 months, 15.2% for >12 months (mean 140 days, range 15–643). Within the analyzable population (ITT >28 days on

Table 6. Clinical response in biological subgroups

Receptor expression in the tumor	Imatinib/vinorelbine					Total number at all dose levels (n = 22)
	600 mg/10 mg/m ² (n = 3)	400 mg/10 mg/m ² (n = 5)	400 mg/15 mg/m ² (n = 5)	400 mg/20 mg/m ² (n = 4)	400 mg/25 mg/m ² (n = 5)	
KIT	2/3 positive: 1 × SD, 1 × PD 1/3 negative: 1 × PR	0 positive 5/5 negative: 1 × PR, 1 × SD, 3 × PD	0 positive 5/5 negative: 1 × PR, 4 × SD	1/4 positive: 1 × SD 3/4 negative: 1 × SD, 2 × PD	4/5 positive: 3 × SD, 1 × PD 1/5 negative: 1 × SD	7/22 positive: 5 × SD, 2 × PD 15/22 negative: 7 × SD, 5 × PD, 3 × PR
PDGF-α	2/3 positive: 1 × PR, 1 × SD 1/3 negative: 1 × PD	5/5 positive: 1 × PR, 1 × SD, 3 × PD	5/5 positive: 1 × PR, 4 × SD	4/4 positive: 2 × SD, 2 × PD	4/5 positive: 3 × SD, 1 × PD 1/5 negative: 1 × SD	20/22 positive: 3 × PR, 11 × SD, 6 × PD 2/22 negative: 1 × SD, 1 × PD
PDGF-β	0 positive 3/3 negative: 1 × PR, 1 × SD, 1 × PD	1/5 positive: 1 × PD 4/5 negative: 1 × PR, 1 × SD, 2 × PD	0 positive 5/5 negative: 1 × PR, 4 × SD	0 positive 4/4 negative: 2 × SD, 2 × PD	0 positive 5/5 negative: 4 × SD, 1 × PD	1/22 positive: 1 × PD 21/22 negative: 3 × PR, 12 × SD, 6 × PD

Correlation of receptor expression with clinical response. Overall biological subgroups are too small for statistical analysis. KIT-positive tumors appear to have a less favorable prognosis than KIT-negative tumors. PDGFR-α and -β are not differentially expressed. Therefore, the influence of receptor expression on response cannot be proven.

study medication'), the RR was 13.6%, the CBR 72.7% (table 5), and the median TTP 176 days. At the date of the data cutoff, 1 patient was still on study medication (since 644 days) with SD (fig. 1). The response was independent of the receptor status (PDGFR-α, -β, and KIT; table 6).

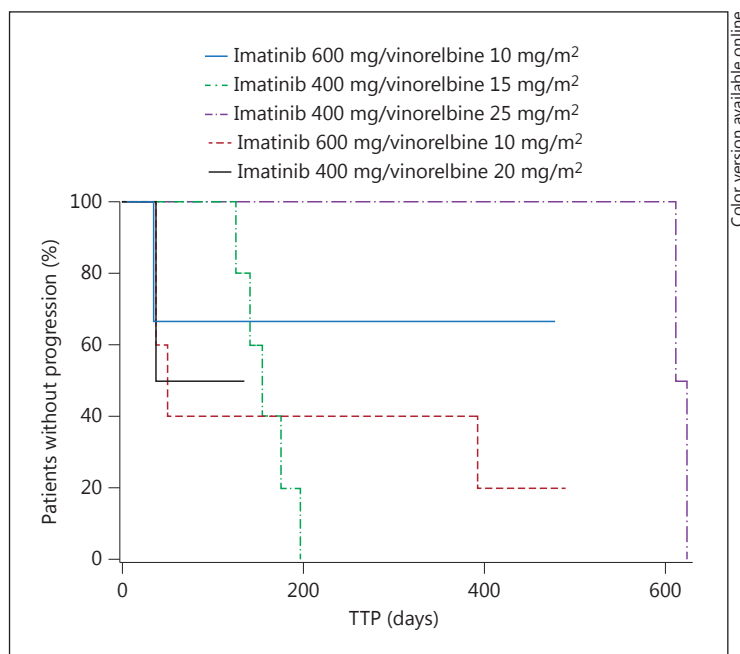
Discussion

This phase I/II dose escalation trial is the first to report on the combination of imatinib mesylate and vinorelbine in the treatment of advanced and/or MBC.

After the amended reduction of the imatinib dose from 600 to 400 mg daily for tolerability reasons, dose escalation could be performed at the 100% level consisting of 400 mg imatinib and 25 mg/m² vinorelbine. Whilst the incidence of AEs causing study drug discontinuation showed no clear dose-dependent increase in the 400 mg imatinib + vinorelbine regimens, dose adjustment or study drug interruption due to AEs was more frequently required with an increasing vinorelbine dose. No drug-related serious AEs (SAEs) were observed in the 400 mg imatinib + vinorelbine regimens. None of the four deaths was drug related.

Although the RR with complete or partial remission in these patients with progressive or MBC was fairly low, a substantial number of patients across all dose levels showed clinical benefit. Patient numbers are too small to correlate drug dose with response or CBR. Expression of PDGFR-α and -β were not differential as 20 of 22 cases were PDGFR-α positive and 21 of 22 PDGFR-β negative. KIT-positive (7 of 22) cases had a less favorable prognosis than KIT-

Fig. 1. Kaplan-Meier curves of the TTP by treatment and efficacy of the analyzable population. Due to the low number of cases, the Kaplan-Meier estimates for the time to response in the subgroups were not conclusive.



negative cases. A statistical correlation of growth receptor expression could not be performed as the numbers in the biological subgroups were too small.

As in previous trials (combining imatinib with capecitabine or docetaxel), the relevant toxicities were similar to the toxicities seen in this trial [21, 22]. The combination of imatinib and vinorelbine commonly caused significant hematologic and gastrointestinal side effects (nausea) as well as fatigue with no clear correlation with the dosage. It is not possible to assign specific AEs to one of the drugs, although in the first cycle all patients were on single-agent imatinib for 1 week before vinorelbine was started. In this first week on trial, the most common side effects were moderate nausea and vomiting. All other effects must be attributed to the combination of the two drugs. Differences in quality of life in the different dose levels are statistically not meaningful. At baseline, 10 patients (55.6%) presented with an ECOG status of 0 and 8 patients (44.4%) with a status of 1. At week 13, 1 patient (14.3%) had an ECOG status of 0 and 6 patients (85.7%) a status of 1.

In studies investigating single-agent i.v. vinorelbine after previous chemotherapy in MBC, the RR was 35.7%, the CBR 65.7%, and the TTP approximately 126 days [29, 30]. Two phase II trials of single-agent imatinib mesylate in heavily pretreated MBC resulted in no clinical responses [17, 18]. As single-agent activity among tyrosine kinase inhibitors has often been only modest in breast cancer, it was anticipated that the combination of imatinib mesylate and vinorelbine, based on preclinical studies suggesting synergy, would lead to encouraging results. Previous trials investigating combinations of imatinib and other chemotherapies did not show a better clinical activity compared to chemotherapy alone. A phase II trial investigated the combination of capecitabine and imatinib and resulted in an RR of 11% and a CBR of 52%, without an enhanced efficacy compared to capecitabine alone [22]. Another phase II trial with imatinib and paclitaxel resulted in an RR of 13.2% and a CBR of 47.4%; the TTP was 119 days [23]. A phase II trial of imatinib and docetaxel resulted in an RR of 22% and a CBR of 67% [21]. Within the analyzable, partially heavily pretreated population of this study, the RR was 13.6%, the CBR was 72.7%, and the median TTP was 176 days. None of the other studies with combinations of imatinib with chemotherapy showed a better efficacy

than the combination in this trial. In addition, RR and CBR were not superior, and the TTP in this combination study of imatinib and vinorelbine was remarkably longer (176 vs. 126 days).

Although the RR in these patients with progressive or MBC was low, the rate of patients who showed a clinical benefit was high. A number of patients across all dose levels showed clinical benefit for as long as 644 days. To allow a better patient selection and prediction of response, further correlative studies are ongoing.

Conclusion

After the reduction of the imatinib dose from 600 to 400 mg daily for tolerability reasons, dose escalation could fully be performed. Nondose-related SAEs were observed in the 400 mg imatinib + vinorelbine regimens. Although the rate of PR or CR in these patients with progressive or MBC was low, over 70% of the patients across all dose levels showed clinical benefit (response or SD) and an improved TTP. Correlative studies exploring biological subgroups further are ongoing and could help to better select patients for a therapy with imatinib and vinorelbine.

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