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CLINICAL TRIAL REPORT

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# Combination vinorelbine and capecitabine for metastatic breast cancer using a non-body surface area dosing scheme

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**Abstract** *Purpose*: This study sought to determine the maximum tolerated dose of flat-dosed vinorelbine in combination with capecitabine in patients with metastatic breast cancer. At the time of study initiation, it was anticipated that vinorelbine would be developed as an oral capsule. A flat dosing scheme of both drugs was used to facilitate development of the oral regimen, and because neither drug's clearance is associated with body surface area (BSA), pharmacokinetic and pharmacogenetic endpoints were explored. *Experimental Design*: Capecitabine was administered orally at 3,000 mg/day on days 1–14. The starting dose of vinorelbine was 20 mg intravenously on days 1 and 8 of a 21-day cycle. The vinorelbine dose was escalated until dose limiting toxicity (DLT). Vinorelbine pharmacokinetics were measured after the first dose. Patients underwent genotype analysis for polymorphisms in the CYP3A5 gene, and the erythromycin breath test (ERMBT), a phenotypic test of CYP3A enzyme activity. *Results*: Twenty five eligible patients were enrolled. Hematologic DLT was seen at the 50 and 45 mg vinorelbine doses; thus the recommended dose is 40 mg on days 1 and 8. Response rate was 30%, and disease stabilization rate was 64% (all dose levels included). Vinorelbine clearance was not associated with ERMBT, BSA, or age. CYP3A5 genotype in this small sample did not have an obvious relationship to clearance or toxicity. *Conclusions*: A non-BSA based dosing scheme of capecitabine and vinorelbine is safe and efficacious. BSA did not affect vinorelbine clearance. We recommend future studies with capecitabine and/or vinorelbine to compare the safety and efficacy of flat dosed versus BSA-dosed treatment.

**Keywords** Clinical pharmacology · Genotype–phenotype correlations · Phase I clinical trial · Erythromycin breath test

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## Introduction

The primary goals of treatment of metastatic breast cancer are: (1) to improve quality of life by palliation of symptoms, and (2) to lengthen survival. These goals are most readily met in patients with hormone-responsive tumors by the use of low-toxicity endocrine therapies. Unfortunately, approximately 30% of breast cancers are hormone receptor negative, and eventually hormone-responsive metastatic disease becomes refractory to endocrine manipulations. In hormone-refractory patients, combination chemotherapy results in higher response rates, longer times to progression [23], and in some studies prolonged overall survival [18], when compared to single agent therapy. Unfortunately, these benefits are often countered by increased toxicity and complexity of the regimen [16]. An effective combination chemotherapy regimen that is both simple and has low toxicity would be of value.

Vinorelbine has been examined in combination with 3–5 day infusions of fluorouracil in advanced breast cancer [6–9]. This combination has been well tolerated, with response rates from 47–62% (both first line and previously treated patients) [6–9]. However, continuous

infusions of 5-fluorouracil are inconvenient due to the need for a portable infusion pump and permanent venous access devices. Daily oral administration of chemotherapeutic agents is much more convenient for patients. Capecitabine, a nucleoside prodrug of 5-fluorouracil with excellent oral bioavailability, is active in patients with previously treated [3] or untreated [19] metastatic breast cancer. The tolerability of vinorelbine and capecitabine as single agents, their non-overlapping toxicity profiles, and the previously demonstrated efficacy of vinorelbine combined with continuous infusion of fluorouracil makes this an attractive drug combination to evaluate further in metastatic cancer. At the time we initiated this study, it was anticipated that vinorelbine, which has an excellent bioavailability profile, was going to be developed as an oral capsule as well.

Normalizing drug doses to body surface area (BSA) is the traditional approach to oncology drug dosing, but in many cases it is not scientifically supportable [2, 20, 22]. This dosing approach has been validated for drugs formulated in vehicles that cause drug volume distribution to be similar to total blood volume (such as paclitaxel solubilized in polyoxyethylated castor oil)[24]. In these cases, BSA is possibly acting as a surrogate for drug volume of distribution (Vss), since Vss approximates total blood volume, which approximates BSA [24, 29].

It has been demonstrated that capecitabine clearance is unrelated to BSA [2, 4].Variability in capecitabine pharmacokinetics is likely to be primarily due to variability in the activity of the enzymes involved in capecitabine metabolism, and not body size [21]. Likewise, clearance of drugs primarily metabolized by the liver, such as vinorelbine, is not correlated with BSA [22]. Plasma clearance of vinorelbine is high, approaching hepatic blood flow in humans, and its volume of distribution is large, indicating extensive extravascular distribution [26]. For these reasons, we hypothesized that BSA-based dosing of capecitabine and vinorelbine was unnecessary. Thus, with the goal of increasing safety and convenience, this study utilized a flat dosing scheme of both capecitabine and vinorelbine. The dose of vinorelbine was escalated based on a pharmacodynamic toxicity, myelosuppression.

The metabolism of vinorelbine has been shown to be mediated by hepatic cytochrome P450 isoenzymes in the CYP3A subfamily.[10] This subfamily plays a dominant role in the metabolism of more drugs than does any other biotransformation enzyme. However, CYP3A expression varies due to environmental stimuli (such as smoking, drug intake or diet), by disease state (such as hepatic dysfunction), and by genetic mutations. Genetic variations in the CYP3A4 gene have not been shown to be related to differences in CYP3A-dependent drug clearance. However, polymorphisms in CYP3A5 have been shown to cause variation in metabolism of such drugs as cyclosporine[17] and midazolam.[5] The mutant allele, CYP3A5*3[8] is associated with low CYP3A5 protein and this allele frequency varies from 50% in African Americans to 90% in Caucasians.[12]

As exploratory endpoints, CYP3A5 genotype analysis and vinorelbine pharmacokinetics were performed, and vinorelbine clearance was correlated with age, BSA, and the erythromycin breath test (ERMBT). The ERMBT has previously been shown to predict steady state trough blood levels of drugs which are CYP3A substrates [11]. We hypothesized that homozygosity for CYP3A5*3 and low ERMBT would be associated with reduced clearance of vinorelbine.

## Patients and methods

### Entry criteria

Eligible patients had metastatic breast cancer, with measurable or evaluable disease by RECIST criteria. Karnofsky performance status was ≥70, and patients had normal hematologic, renal, and hepatic function defined as ANC > 1500, platelet count > 100 K, calculated creatinine clearance > 60 ml/min, AST/ALTPatients were excluded if they had previous treatment with continuous infusion or daily oral administration of fluorouracil, capecitabine, or vinca alkaloids and if they had baseline Grade 2 or greater peripheral neuropathy, or if they were pregnant or nursing. Patients who required concurrent treatment within 7 days prior to initial vinorelbine with drugs known to induce or inhibit CYP3A activity were also ineligible. Excluded drugs included midazolam, anti-mycotic agents (ketoconazole and related compounds), macrolide antibiotics (erythromycin and related compounds), nifedipine, anti-seizure drugs, H2 blockers, grapefruit juice, and rifampin.All patients signed an informed consent regarding the experimental nature of this therapy after approval by the University of Michigan Institutional Review Board and in accordance with an assurance filed with and approved by the Department of Health and Human Services.

### Treatment plan

This study was a Phase I/II study of the combination of oral capecitabine and weekly intravenous vinorelbine. Eligible patients were identified from the patient population of the University of Michigan Health System.

Both agents were given flat doses regardless of BSA. All chemotherapy was delivered on a 21-day cycle. Capecitabine was administered orally at 1,500 mg twice daily (3000 mg/day) on days 1–14. The starting dose of vinorelbine was 20 mg administered intravenously weekly on days 1 and 8. The dose was escalated in 10 mg increments until dose limiting toxicity (DLT), which was defined as Grade 3 or 4 toxicities (non-hematologic), or Grade 3 or 4 thrombocytopenia at any time during the first cycle. Neutropenia was considered dose-limiting if it reached Grade 3 or 4 on day 21 in the first cycle. Once DLT was defined, an intermediate dose level (−5 mg)

was tested, and if more than one-sixth of the patients had DLT, the next lower dose level was used. The recommended Phase II dose was the dose at which one of six or fewer patients experienced DLT. Subsequently, eight additional patients were treated at the Phase II dose in order to increase the sample size for secondary analyses.

Prior to study treatment, the ERMBT was administered in the outpatient setting within 2 weeks of the first dose of vinorelbine, performed as previously described.[27] Patients had blood drawn for pharmacokinetic analysis after the first administration of vinorelbine. Blood was collected before infusion, immediately at the end of infusion, and at 20, 45, 75 min after infusion, then at 2, 3, 4, 6, 8 12, 24, 36, 48, and 72 h. Blood samples were analyzed for vinorelbine with a liquid chromatography with mass spectrometry method as described previously.[25] Pharmacokinetic parameters were calculated using standard non-compartmental methods.

### CYP3A5 Genotype determination

DNA was extracted from whole blood using the Qiagen DNeasy® Tissue kit and the QIAamp® DNA Blood Midi kit (Qiagen Inc., Valencia, CA, USA), respectively, according the manufacture's instructions and the yield was determined by spectrophotometry (Beckman DU 640; Beckman Coulter, Inc., Fullerton, CA, USA). DNA samples were assayed for the common CYP3A5*3 genetic polymorphism using polymerase chain reaction–restriction fragment length polymorphism (PCR-RFLP) assay as described previously [9].

## Results

### Dose escalation and toxicity

A total of 25 eligible patients were enrolled; all were Caucasian with 24 females and 1 male. Patient characteristics are described in Table 1. The flat-dosed capecitabine was well tolerated, as there were no instances of Grade 3 hand–foot syndrome or diarrhea. Three patients had a dose reduction for Grade 2 capecitabine toxicity, including hand–foot syndrome and diarrhea. There was no apparent relationship between BSA and necessity for dose reduction of capecitabine.

The vinorelbine dose was escalated as described in Table 2. All 25 patients completed at least two cycles of treatment, and no patient discontinued therapy due to toxicity. Three patients were treated at the 20 , 30 , and 40 mg dose levels with no DLT. At both the 50 mg and 45 mg dose levels, there were two hematologic DLTs (Table 2).

**Table 1** Patient characteristics

| | |
|---|---|
| Number of eligible patients | 25 |
| Average patient age (years) | 50 (29–69) |
| Number with measurable disease | 20 (80%) |
| Number: prior chemotherapies for metastatic disease | |
| 0 | 10 (40%) |
| 1 | 12 (48%) |
| 2 | 3 (12%) |
| Prior anthracycline | 23 (92%) |
| Prior taxane | 25 (100%) |
| Hormone receptor status | |
| Positive | 16 (64%) |
| Negative | 9 (36%) |

### Efficacy

Twenty of 25 (80%) patients had disease that was measurable by RECIST criteria. Overall, six of the patients with measurable disease responded [30, 95% CI (11.9–54.3)], with one complete response. Nine of 25 patients progressed within the first 12 weeks of treatment (36, 95% CI [18.0–57.5]), and the remaining 16 patients had stable disease or better for over 12 weeks, with a clinical benefit rate of 64, 95% CI (42.5–82.0).

### Pharmacokinetics

Pharmacokinetic analysis of vinorelbine was performed on the last 13 patients enrolled in the study, including 5 patients treated at 45 mg/week, and 8 patients treated at 40 mg/week. The mean vinorelbine clearance of the

**Table 2** Genotype, ERMBT, body surface area (BSA), and dose limiting toxicity (DLT)

| Patient | Genotype | ERMBT | BSA ($m^2$) | Vinorelbine dose (mg) | DLT |
|---|---|---|---|---|---|
| 1 | NA | 3.01 | 1.69 | 20.0 | none |
| 2 | *3/*3 | 1.44 | 1.75 | 20.0 | none |
| 3 | wt/*3 | 2.71 | 1.62 | 20.0 | none |
| 4 | *3/*3 | 2.83 | 1.90 | 30.0 | none |
| 5 | wt/*3 | 2.89 | 1.73 | 30.0 | none |
| 6 | *3/*3 | 3.74 | 1.65 | 30.0 | none |
| 7 | wt/*3 | 3.09 | 1.59 | 40.0 | none |
| 8 | wt/*3 | 1.58 | 2.40 | 40.0 | none |
| 9 | *3/*3 | 3.48 | 1.99 | 40.0 | none |
| 10 | *3/*3 | 3.81 | 1.75 | 50.0 | Low ANC |
| 11 | *3/*3 | 4.19 | 2.03 | 50.0 | none |
| 12 | *3/*3 | 1.77 | 1.78 | 50.0 | Low ANC |
| 13 | *3/*3 | 3.05 | 1.72 | 45.0 | none |
| 14 | wt/*3 | 3.32 | 1.74 | 45.0 | none |
| 15 | *3/*3 | 2.35 | 1.69 | 45.0 | none |
| 16 | *3/*3 | 2.06 | 1.70 | 45.0 | Low ANC |
| 17 | *3/*3 | 2.07 | 1.78 | 45.0 | Low ANC |
| 18 | *3/*3 | 2.75 | 1.56 | 40.0 | none |
| 19 | *3/*3 | 3.03 | 1.72 | 40.0 | none |
| 20 | *3/*3 | 1.90 | 2.29 | 40.0 | none |
| 21 | *3/*3 | 2.87 | 1.60 | 40.0 | none |
| 22 | *3/*3 | 0.86 | 2.12 | 40.0 | none |
| 23 | *3/*3 | 3.15 | 1.67 | 40.0 | none |
| 24 | *3/*3 | 1.62 | 1.77 | 40.0 | none |
| 25 | *3/*3 | 2.57 | 1.60 | 40.0 | none |

population was 57.7 l/h (SD 12.7 l/h), similar to that reported in the literature (Table 3) [13, 15, 26]. Clearance in l/hr was found to be unrelated to BSA, age, or ERMBT (Fig. 1). Vinorelbine was found to have a large volume of distribution at steady state (Vss) of 1,428 l (SD 510 l), as previously reported. BSA showed no relationship to Vss of vinorelbine (Fig. 2).

### CYP3A5 genotype

All patients were genotyped for the common CYP3A5*3 polymorphism. None of the patients were homozygous wild-type, while 20% ($n = 5$) were heterozygous CYP3A5*1/*3 and 80% ($n = 20$) were homozygous variant CYP3A5*3/*3. the results consistent with known allelic frequencies [11]. Low ERMBT result did not predict heterozygous CYP3A5 genotype (Fig. 2).

## Discussion

Our data demonstrate the feasibility and safety of flat dosing of capecitabine and vinorelbine in a typical metastatic breast cancer population. For this combination therapy we recommend flat-dose capecitabine 1,500 mg twice daily plus vinorelbine 40 mg on day 1 and day 8 as being efficacious and tolerable. In comparison with other trials of this combination, the median BSA of our patient population was 1.74 $m^2$, and the average per-meter-squared dose of capecitabine delivered was 1,724 mg/$m^2$ on days 1–14 (range 1,250–1887 mg/$m^2$). The recommended dose of vinorelbine in our study averages 23 mg/$m^2$ on days 1 and 8, of a 21-day cycle. Three Phase I studies of vinorelbine and capecitabine combination therapy in metastatic breast cancer have been published. Two of the studies ultimately recommended doses of capecitabine of 2,000 mg/$m^2$/d and vinorelbine 25 mg/$m^2$ on days 1 and 8 [14, 28]; the other study in elderly patients recommended capecitabine 1,250 mg/$m^2$/d and vinorelbine 20 mg/$m^2$ on days 1 and 8.[6]

Our patient population primarily included patients being treated first- or second-line with chemotherapy, but all had received prior taxanes and most had also received prior anthracyclines, either in the metastatic or adjuvant setting. The historical data would suggest a 20%–30% response rate from single agent capecitabine in this population [3, 19]. The observed 30% response rate and 65% disease stabilization rate compares favorably to the historical sample, despite the escalating doses of vinorelbine received by the patients, with minimal hematologic or non-hematologic toxicity.

The *a priori* hypothesis was that there would be no association between toxicity of the flat-dosed combination regimen with BSA, and this hypothesis is supported by our data. We also found no association between BSA and clearance of vinorelbine, as has been previously shown with capecitabine [4]. This is not surprising, since the impact of BSA on the variability in drug pharmacokinetics is more likely to be apparent for drugs where the distribution is similar to total blood volume (and thus to BSA).

Despite the fact the vinorelbine is largely metabolized by P450 enzymes of the CYP3A subfamily[10], there was also no association noted between the ERMBT, vinorelbine clearance, or toxicity. This observation suggests that the ERMBT would not be a useful test in tailoring the dose of vinorelbine to an individual's metabolic phenotype, in contrast to our finding in a prior study of the ERMBT and docetaxel [7].

Only five patients in our population were heterozygous for the CYP3A5*3 allele while the remainder were homozygous CYP3A5*3. The CYP3A5*3 allele codes for an aberrantly spliced mRNA with a premature stop codon, therefore, patients with two CYP3A5*3 alleles exhibit a nearly complete lack of CYP3A5 protein expression [11]. We hypothesized that increased vinorelbine clearance and decreased toxicity would correlate with homozygosity for the wild-type CY3A5 allele (*1) and less so with CYP3A5*1/*3. Since our study had $n = 0$ homozygous wild-type CYP3A5*1 and only $n = 5$ heterozygous CYP3A5*3 patients, the lack of any genotype/phenotype association makes a false negative result highly likely. A larger study is needed to confirm these results.

**Table 3** Vinorelbine pharmacokinetics in the study population

| Vinorelbine dose (mg) | $AUC_{(0\text{-}t)}$ (h*ng/ml) | $AUC_{(0\text{-}\infty)}$ (h*ng/ml) | CL (l/h) | $C_{max}$ (ng/ml) | $T_{max}$ (h) | $T_{1/2}$ (h) | Vss (l) |
|---|---|---|---|---|---|---|---|
| 45.0 | 900.0 | 936.1 | 48.1 | 860.6 | 0.25 | 19.1 | 876.0 |
| 45.0 | 649.1 | 693.4 | 64.9 | 1000.6 | 0.15 | 31.9 | 1487.5 |
| 45.0 | 604.0 | 643.8 | 69.9 | 1073.0 | 0.15 | 35.6 | 1628.5 |
| 45.0 | 853.8 | 878.4 | 51.2 | 1185.8 | 0.17 | 23.6 | 885.7 |
| 45.0 | 762.3 | 806.8 | 55.8 | 918.5 | 0.17 | 33.0 | 1219.8 |
| 40.0 | 941.9 | 975.9 | 41.0 | 1516.7 | 0.17 | 25.2 | 744.7 |
| 40.0 | 625.5 | 665.9 | 60.1 | 598.1 | 0.27 | 26.2 | 1873.8 |
| 40.0 | 599.0 | 641.8 | 62.3 | 633.7 | 0.17 | 31.3 | 1553.6 |
| 40.0 | 959.6 | 1002.0 | 39.9 | 965.3 | 0.18 | 25.3 | 850.2 |
| 40.0 | 770.2 | 850.3 | 47.0 | 294.0 | 0.25 | 26.6 | 1330.6 |
| 40.0 | 679.7 | 767.3 | 52.1 | 1410.9 | 0.18 | 53.9 | 1677.0 |
| 40.0 | 395.7 | 440.7 | 90.8 | 360.8 | 0.18 | 46.6 | 2777.6 |
| 40.0 | 559.5 | 602.8 | 66.4 | 670.5 | 0.18 | 31.8 | 1657.6 |

*$AUC_{(0\text{-}\infty)}$* systemic exposure; *CL* mean plasma clearance; ***$C_{max}$*** maximum concentration; ***$T_{max}$*** time to maximum concentration; $t_{1/2}$ terminal phase half-life; *Vss* volume of distribution at steady state

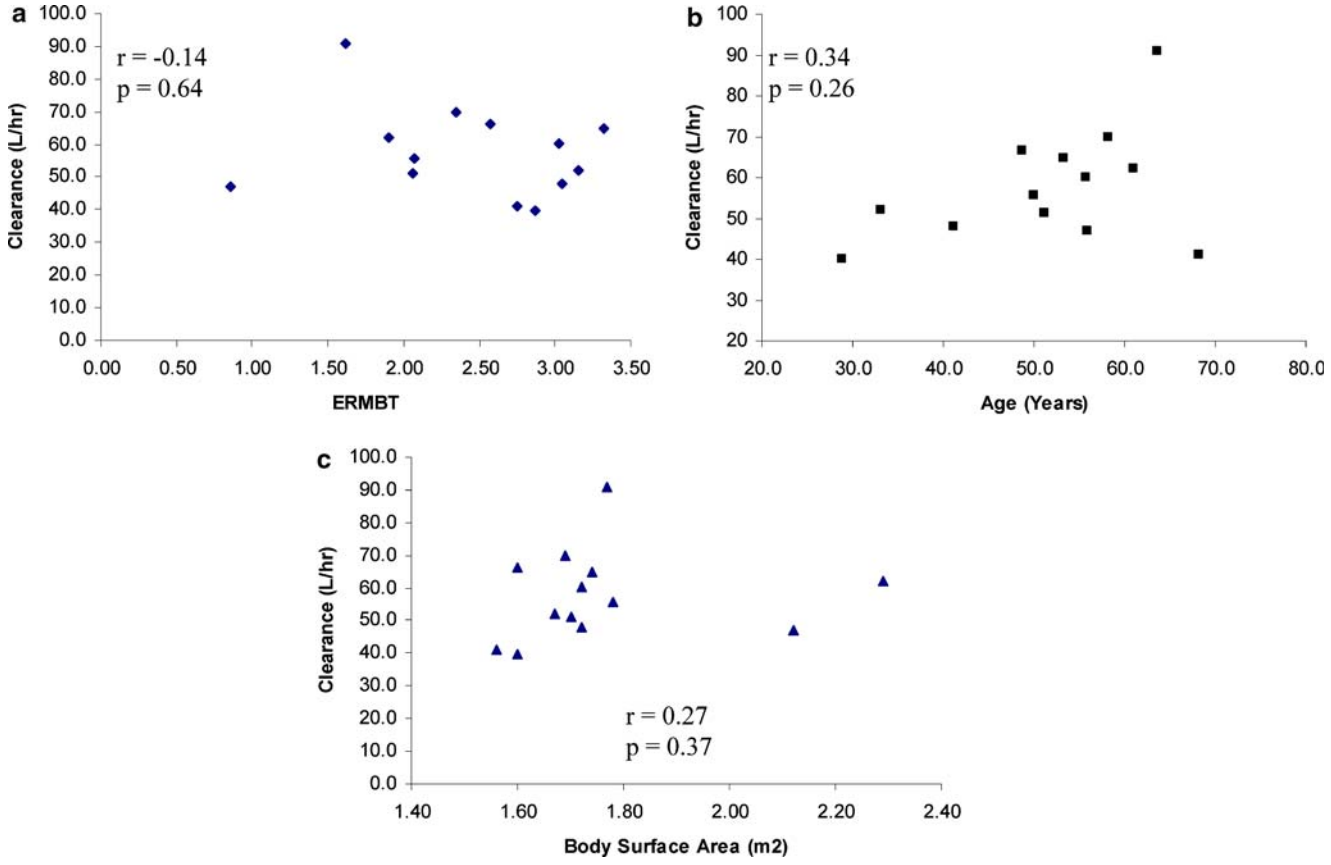


**Fig. 1** Lack of relationship of Erythromycin breath test (ERMBT) (**a**) age or (**b**) body surface area (**c**) to vinorelbine clearance

In conclusion, this study demonstrates that a non-BSA-based dosing scheme of capecitabine and vinorelbine is safe and efficacious. Based on these data, we recommend future studies with capecitabine and/or vinorelbine to compare the safety and efficacy of flat-dosed versus BSA-dosed treatment. We cannot determine from this Phase I study whether this combination therapy is more effective than single-agent sequential vinorelbine or capecitabine, and a randomized Phase III study would have to be performed in order to make this treatment a standard recommendation [1] If vinorelbine is ever developed as an oral formulation, further study of this combination therapy is clearly indicated.

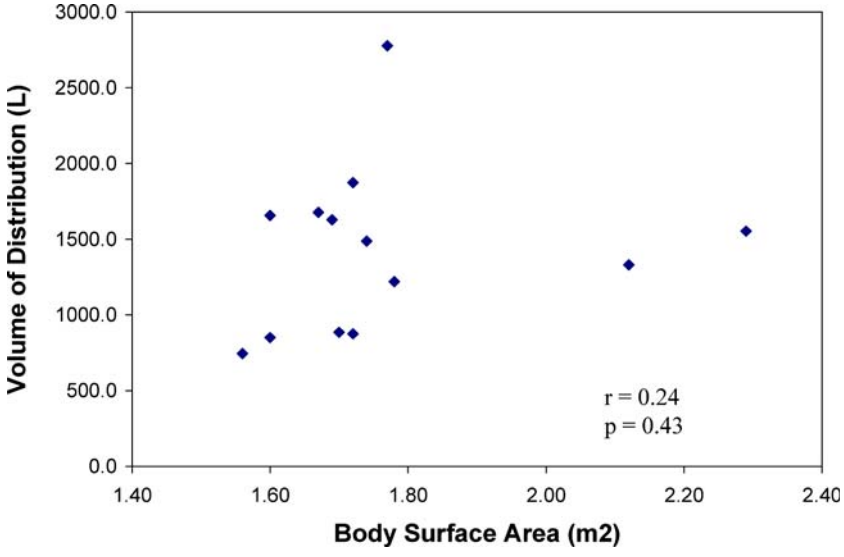


**Fig. 2** Volume of distribution of vinorelbine is unrelated to body surface area (BSA)

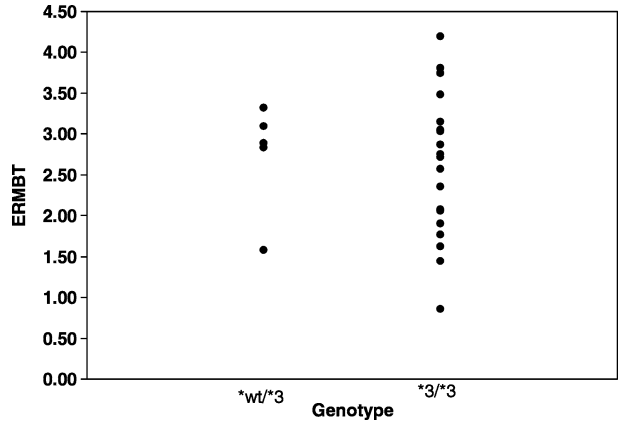


**Fig. 3** ERMBT results in the heterozygous and homozygous mutant genotypes seen

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