Current Status of Vinorelbine For Breast Cancer

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Vinorelbine tartrate (Navelbine) is a new semisynthetic vinca alkaloid with efficacy against a variety of solid tumors, including non-small-cell lung cancer, breast cancer, head and neck cancer, and Hodgkin's lymphoma.

Introduction

Vinorelbine tartrate (5'-noranhydro-vinblastine) is a new semisynthetic vinca alkaloid with a broad spectrum of in vitro antitumor activity demonstrated in preclinical studies. Phase I/II trials confirmed the efficacy of this drug against a variety of solid tumors, including non-small-cell lung cancer, breast cancer, head and neck cancer, and Hodgkin's lymphoma. Favorable phase III trial results led to its recent FDA approval for use as a first-line agent in ambulatory patients with advanced non-small-cell lung cancer.

After nearly a decade of clinical trials in Europe and recent studies in the United States, there is now extensive data confirming the activity of vinorelbine for metastatic breast cancer. Vinorelbine differs from other vinca alkaloids, for the drug possesses unique pharmacokinetics and a more favorable side-effect profile. This article will review the encouraging results of single agent and combination therapy trials, compare vinorelbine activity to established therapies for breast cancer, consider novel routes of administration, and discuss ongoing randomized clinical trials and future studies that may lead to the widespread use of vinorelbine for the treatment of breast cancer.

Pharmacokinetics

The chemical structure of vinorelbine differs from the other members of the vinca alkaloid family (such as vincristine or vinblastine), in that vinorelbine has a substitution on the catharine ring of the molecule instead of the vindoline nucleus. This difference imparts the unique biochemical properties of the drug, and vinorelbine pharmacokinetics thus differ from the other vinca alkaloids.

Vinorelbine is highly lipophilic, which results in more significant tissue uptake and a greater therapeutic index than the other vinca alkaloids. The excretion of vinorelbine following a dose of 30 mg/m² infused over 15 to 20 minutes has been described as triphasic, with a large volume of distribution, high systemic clearance, and prolonged terminal phase due to the slow efflux of the drug from peripheral tissue compartments [1]. The terminal half-life of vinorelbine is 27.7 to 43.6 hours, and the mean plasma clearance ranges from 0.83 to 1.26 L/h/kg [2,3].

Metabolism and Elimination

Vinorelbine is metabolized predominantly by the liver, with most of the drug and its metabolites eliminated via the biliary tract and excreted in feces. In fact, the clearance of vinorelbine approaches hepatic blood flow (1.3 L/h/kg) [1]. Renal clearance accounts for only 10% to 12% of total drug elimination [2]. To date, the effect of hepatic or renal dysfunction on vinorelbine metabolism has not been determined, but dose reduction is recommended for patients with liver function abnormalities. The hepatic cytochrome P-450 3A enzyme system appears to be responsible for the metabolism of vinorelbine, all vinca alkaloids, and the majority of chemotherapeutic agents [4-6]. One vinorelbine metabolite, deacetylvinorelbine, has been detected in plasma and possesses antitumor activity [1]. Specific drugs have been shown to inhibit vinorelbine metabolism by competitive inhibition of P-450 3A, especially other vinca alkaloids and drugs such as doxorubicin, methotrexate, and calcium-channel blockers [4-6].

Research has demonstrated large variation between patients in the pharmacokinetics of vinorelbine, but the reasons for this diversity are unknown. Although age does not appear to influence vinorelbine pharmacokinetics [1], there is growing evidence that the activity of the P-450 3A enzyme may be altered with menopause [7]. As a result, investigators are currently studying the potential impact of menopausal status on vinorelbine metabolism.

Potential Mechanisms of Resistance
Like other vinca alkaloids, vinorelbine resistance is presumably mediated by multidrug resistance (MDR) and P-glycoprotein overexpression, which results in enhanced drug efflux from tumor cells [8,9]. The precise mechanism of resistance to vinorelbine has yet to be determined, but the role of MDR is supported by evidence that there appears to be substantial cross-resistance between vinorelbine and other members of the vinca family, as well as a variety of other MDR substrates [10].

**Mechanism of Action**

Vinorelbine inhibits microtubule assembly, and thus, is cell-cycle-specific. Like other vinca alkaloids, vinorelbine blocks formation of the mitotic spindle apparatus at metaphase and prevents cell division. This is in contrast to the taxanes, such as paclitaxel (Taxol), which promote and stabilize the assembly of microtubules after spindle formation has occurred.

One of the most promising aspects of vinorelbine relates to this selective effect on microtubules. Peripheral neuropathy is common with most vinca alkaloids, and is believed to result from a direct effect on the microtubules in peripheral nerves. However, in vitro immunofluorescence experiments have demonstrated that vinorelbine is selective for nonneural microtubules [11]. Additional studies have confirmed that toxicity against axonal microtubules typically occurs at a significantly higher vinorelbine concentration (30 to 40 mol/L) than is required for maximal antitumor effect (5 mol/L) [11,12]. Therefore, as expected from preclinical data, vinorelbine has a wide therapeutic window, which has resulted in reduced neurotoxicity in clinical trials compared to the other vinca alkaloids.

**Toxicity**

Extensive clinical studies have been conducted to elucidate the safety profile of vinorelbine. Table 1 lists the major toxicities of vinorelbine reported in three North American clinical trials involving 222 women with metastatic breast cancer [13,14].

**Hematologic Effects**

The majority of the adverse events reported in these trials were hematologic. Neutropenia was the most commonly reported toxicity, with 96% of women having an absolute neutrophil count (ANC) < 2,000/mm³ with single-agent treatment and 41% of women experiencing an ANC < 500/mm³. Fever and neutropenia were reported in 9% of treatment cycles. Recovery from hematologic toxicity is rapid, with nadirs typically occurring at 7 to 10 days and complete recovery 1 to 2 weeks later in most cases.

Although neutropenia remains the most frequent cause of dose adjustment or treatment delay in patients who receive weekly vinorelbine administration, growth factor support has not been routinely recommended for weekly 30-mg/m² doses of vinorelbine when used as a single agent. However, combination regimens that include vinorelbine may require granulocyte colony-stimulating factor (G-CSF; filgrastim [Neupogen]) to minimize this additive toxicity and to maintain the dosage schedule.

Vinorelbine also resulted in mild anemia in clinical trials, with 87% of women with breast cancer having a hemoglobin of less than 11 mg/dL. Despite the frequency of this adverse effect, however, transfusion was seldom necessary. Finally, thrombocytopenia was rarely reported; fewer than 10% of administered cycles were associated with platelet counts below 100,000/mm³.

**Nonhematologic Effects**

In contrast to its significant myelosuppression, vinorelbine is associated with only modest nonhematologic toxicity. The drug produced mild elevations of serum liver function tests, with abnormal serum glutamic-oxaloacetic transaminase (SGOT) noted more commonly than an increased total bilirubin. However, clinical symptoms or frank hepatic toxicity has not been reported. Vinorelbine is only mildly emetogenic, and coadministration of potent serotonin antagonist antiemetics is not routinely required. The predominant gastrointestinal side effects included nausea (50%), vomiting (23%), constipation (38%), and diarrhea (20%).

Vinorelbine is a mild vesicant, and local reactions involving phlebitis or pain at the infusion site were reported in approximately 20% of patients. Peripheral neuropathy, characterized by mild to moderate, reversible paresthesias or hypoesthesias, occurred in 30% of women. No grade III or grade IV neurotoxicity was seen, and loss of deep-tendon reflexes was noted in fewer than 5% of patients.

Dyspnea occurred in 9% of patients within hours after vinorelbine administration, and yet pulmonary symptoms were rarely severe and most likely represent an allergic reaction. Finally, alopecia was reported in 12% of women.

In summary, vinorelbine is well tolerated, with the major toxicity involving neutropenia.
Results of Clinical Trials

The efficacy of vinorelbine has been studied extensively in Europe and the United States. Preliminary studies demonstrated significant activity against a variety of solid tumors, including breast cancer [8,15,16]. Based on these promising results, investigators focused on the efficacy of vinorelbine as a treatment for metastatic breast cancer. After phase I results defined the maximum tolerated dose at 27.5 to 35.4 mg/m², numerous phase II trials were initiated in Europe in women with metastatic breast cancer using a standard dose of 30 mg/m²/wk [17]. Table 2 summarizes the phase II experience with vinorelbine in this setting.

Canobbio et al were the first to report on the efficacy of vinorelbine as a treatment for metastatic breast cancer [18]. In their phase II study, 26 patients were evaluated for response after treatment with at least 8 weekly cycles of vinorelbine. The study involved a heterogeneous group of women who had failed to respond to either adjuvant or palliative chemotherapy, and thus the published response rate of 46% with a median response duration of 22 weeks encompassed both first- and second-line therapy.

Second-Line Therapy

Based on the results of the preliminary phase I/II trials, investigators began to study the efficacy of this new drug as a second-line treatment for metastatic breast cancer. Most of these trials were conducted in Europe. Table 2 summarizes the experience with vinorelbine as a second-line therapy in a total of 133 patients [19-21].

Dieras et al published the results of a phase II trial of single-agent vinorelbine in 25 patients with advanced breast cancer who had received a median of two prior chemotherapy regimens [19]. The response rate was 36%, with a median response duration of 28 weeks.

A subsequent trial reported by Gasparini et al involved 67 patients, all of whom had not responded to at least one chemotherapy treatment for metastatic disease [20]. This study used a lower vinorelbine dose (20 to 25 mg/m²), and a median of eight cycles was administered per patient. The overall response rate was 36%, with a median time to progression of 18 weeks. The most significant toxicity was myelosuppression, with 28% of patients experiencing grade III neutopenia and 9%, grade IV neutropenia; this resulted in an average delivered dose intensity of 65% to 70%. Nonhematologic toxicities were uncommon; mild to moderate nausea/vomiting occurred in 22% of patients and grade I or II peripheral neuropathy in 10%. Since this trial demonstrated the activity of vinorelbine in patients who had received prior treatment with either CMF (cyclophosphamide, methotrexate, and fluorouracil) or anthracyclines, it supported the absence of cross-resistance among these agents.

Finally, a US multicenter trial of single-agent vinorelbine reported a modest response rate of 17% and a median duration of response of 18 weeks [21]. Thus, as a second-line treatment, vinorelbine was associated with response rates ranging from 17% to 36% in heavily pretreated patients, with partial responses accounting for most of the total response, and a median response duration of 18 to 22 weeks. Such variability in the results of phase II trials can be explained by the specific response criteria employed, the heterogeneity of patient populations treated, and the inclusion of both single- and multi-institution studies.

First-Line Therapy

Based on the encouraging results of phase II trials in pretreated patients, vinorelbine was subsequently tested as a first-line treatment for metastatic breast cancer. Table 2 also summarizes the cumulative experience with intravenous single-agent vinorelbine used as first-line therapy in a total of 329 patients [21-24]. Not surprisingly, the results are superior to second-line therapy, with higher response rates and a longer duration of response. What is noteworthy, however, is the remarkably consistent overall response rate of 40% to 44% found in single-institution European trials and confirmed by a large US multicenter trial.

In the largest French trial, Fumoleau et al gave vinorelbine as a weekly 30- mg/m² injection to a total of 157 patients [22]. Patients received an average of 11.5 cycles of vinorelbine. The overall response rate was 41%, 7% of which were complete responses and 34% partial responses. When stratified according to the site of measurable disease, response rates were as follows: skin (70%), lymph node (67%), lung (33%), bone (30%), and liver (23%). The median time to treatment failure was 6 months, and the median survival time was 18 months.

The principal toxicity in this study was hematologic, with 72% of patients having at least one episode of grade III or IV neutropenia. Nausea/vomiting, anemia, and thrombocytopenia were seen in less than 1% of cycles, and peripheral neuropathy was experienced by only 3% of patients.

These results were confirmed by Romero et al, who reported the results of single-agent vinorelbine
as a first-line treatment in 45 patients with metastatic breast cancer [23]. The overall response rate was 41%, with a median response duration of 9 months.

In a subsequent US multicenter study, Weber et al treated a total of 106 patients who had measurable disease with vinorelbine (as first-line therapy in 65 patients and as second-line therapy in 41) [21]. Among the patients who received vinorelbine as first-line treatment, the response rate was 40% (26/65) and the median duration of response was 38 weeks.

Table 3 compares the response rates attained with the chemotherapeutic agents most active as first- or second-line therapy for breast cancer [15]. The response rates for vinorelbine have been compiled from both European and US trials, and the activity depends on the degree of prior treatment. This comparison shows vinorelbine to be one of the most active drugs against breast cancer, perhaps comparable to doxorubicin and paclitaxel.

**Phase III Comparative Trial**

Based on the encouraging phase II results, a phase III trial was initiated to compare vinorelbine to a standard single-agent treatment. This US multicenter trial randomized 179 anthracycline-resistant patients to receive either 30 mg/m² of vinorelbine weekly or 25 mg/m² of melphalan (Alkeran) every 4 weeks as a second- or third-line therapy for advanced breast cancer [25]. Melphalan was chosen as the control arm based on its well-established activity against breast cancer, unknown efficacy in anthracycline-resistant patients, and favorable toxicity profile. The median age of all patients was 53 years; 30% were premenopausal, and 50% were estrogen-receptor-positive.

In this heavily pretreated patient population, vinorelbine produced a significant improvement in time to treatment failure (13 vs 8 weeks), longer time to disease progression (12 vs 8 weeks), greater response rate (16% vs 9%), and a 4-week improvement in survival (35 vs 31 weeks). This trial was the first to demonstrate a survival benefit of vinorelbine treatment in anthracycline-resistant patients with metastatic disease.

The major toxicity of the vinorelbine arm was myelosuppression, with 37% of patients experiencing grade IV neutropenia. However, the authors concluded that compared to other treatments for advanced breast cancer, vinorelbine was well tolerated.

**Combination Regimens**

Due to the activity achieved with single-agent vinorelbine, several investigators launched clinical trials of regimens that combined vinorelbine with other active chemotherapy drugs. Table 4 lists the most active combination regimens; most of these have produced response rates exceeding 50% when used as first-line therapy. However, the improved response rates have come at the expense of greater toxicity.

**Vinorelbine/A anthracycline Combinations**—Most of the clinical trials incorporating vinorelbine into combination regimens for metastatic breast have involved anthracyclines. This is a logical choice, since the anthracyclines have the greatest single-agent activity against breast cancer, have minimal overlapping toxicity with vinca alkaloids other than myelosuppression, and are the mainstay of most standard regimens.

The largest combination trial, reported by Spielmann et al, involved 89 patients who had received no prior treatment for metastatic breast cancer [26]. The regimen consisted of doxorubicin (50 mg/m² given on day 1) plus vinorelbine (25 mg/m² administered on days 1 and 8). Cycles were repeated every 3 weeks. The overall response rate was 74%, with responses noted in both visceral disease (71%) and soft-tissue or bone disease (81%). The median duration of response was 12 months, and the median overall survival duration was 27.5 months.

The major dose-limiting toxicity was neutropenia, with 41% of patients experiencing grade III or IV toxicity and 16% requiring admission to the hospital for febrile neutropenia. Significant cardiac toxicity was seen in 10% of patients, but only in patients who had received prior adjuvant therapy with an anthracycline. Additional side effects of vinorelbine/doxorubicin included nausea and vomiting. Other side effects were encountered rarely. These results were confirmed in a US multicenter trial involving 50 patients with metastatic breast cancer. Use of the same regimen as a first-line treatment produced a 54% overall response rate [27]. Neutropenia was again the major toxicity, with 83% of patients experiencing grade IV neutropenia and 8% of patients admitted to the hospital with febrile neutropenia (including one septic death). This study was designed to administer a maximum cumulative doxorubicin dose of 400 mg/m², and only one patient developed heart failure.

Other investigators have achieved similarly impressive results combining vinorelbine with other anthracyclines, such as epidoxorubicin (Epirubicin) and mitoxantrone (Novantrone). The combination of epidoxorubicin and vinorelbine resulted in a response rate of 46% [28]. Based on hematologic toxicity, this phase I/II study established the recommended dosage regimen as 60 mg/m² of
epidoxorubicin given on day 1, with 25 mg/m² of vinorelbine administered on days 1 and 7. The combination of mitoxantrone (12 mg/m²) and vinorelbine (10 to 12 mg/m²) produced an overall response rate of 56% [29]. When given as first-line therapy for metastatic disease, this combination was associated with higher response rates in the subset of patients who had not been previously exposed to an anthracycline during adjuvant chemotherapy (68% vs 38%). Subsequent investigators have incorporated growth factors to minimize the myelosuppression associated with the combination of vinorelbine and an anthracycline. These studies have demonstrated that the use of G-CSF can prevent significant grade IV neutropenia in patients treated with vinorelbine plus doxorubicin (with each drug given at a dosage of 25 mg/m² on days 1 and 4) [30].

Vinorelbine/Fluorouracil—Fluorouracil has also been used together with vinorelbine. Dieras et al reported the results of a regimen combining a continuous 5-day infusion of fluorouracil (750 mg/m²/d) with vinorelbine (30 mg/m² administered on days 1 and 5) [31]. Among the 63 patients who received this regimen as first-line therapy, the response rate was 67%, median response duration was 9 months, and median survival time was 20 months. As expected, this combination regimen was associated with more pronounced side effects than single-agent treatment. Significant mucositis (> grade II) occurred in 33% of patients and reversible neutropenia (> grade II) in 74%. These adverse reactions prompted dose reductions in 40% of patients.

Vinorelbine/Mitomycin—Vinorelbine has been tested in combination with mitomycin (Mutamycin) as well. Scheithauer et al proposed a regimen consisting of vinorelbine, 30 mg/m² given once every 3 weeks, along with mitomycin, 15 mg/m² given every 6 weeks [32]. Overall, 34% of the 34 patients treated with this regimen responded, with an additional 47% maintaining stable disease. The median survival duration was 8.8 months. This combination, selected due to its minimal overlapping toxicity, was indeed well tolerated as palliative second-line therapy, with only 12% of patients experiencing grade III or IV neutropenia.

Vinorelbine/Paclitaxel—Another regimen that has generated significant interest is vinorelbine plus paclitaxel. This combination, which creates a total microtubule poison, has theoretical advantages due to the potential for synergy when the drugs are given together. Preclinical data have demonstrated that the combination is synergistic in vitro when the drugs are given simultaneously but that antagonism occurs when paclitaxel is administered before vinorelbine [33,34]. Another potential advantage of this combination is that paclitaxel can overcome vinorelbine resistance that may result from mutations in tubulin. However, since both vinorelbine and paclitaxel appear to be MDR substrates, the potential for cross-resistance remains unknown. Preliminary phase I/II research tested a regimen consisting of vinorelbine at a dosage of 25 mg/m² given on days 1 and 8 and paclitaxel, 175 mg/m² administered as a 3-hour infusion on day 1 (personal communication, A.Y. Chang, MD, 1994). After 14 patients were enrolled, further dose escalation was halted due to significant myelosuppression. Neutropenia remains a major impediment to developing a successful vinorelbine/paclitaxel combination regimen. (Neutropenia is the dose-limiting toxicity of both agents.) However, the use of growth factors may overcome this obstacle. Another concern involves the potential for significant additive neuropathy. Investigators have reported cross-resistance and cumulative neurotoxicity confirmed by electrophysiologic testing in patients with a prior history of paclitaxel treatment who were subsequently treated with vinorelbine [35,36]. Several centers are developing phase II vinorelbine/paclitaxel combinations, but based on preliminary data, more experience is needed to minimize neuropathy and myelosuppression. Thus, this combination remains investigational at present.

Other Routes of Administration

While many investigators have explored the role of vinorelbine in combination regimens, other researchers have focused on methods to improve the effectiveness of this drug through alternate routes of administration, such as oral dosing or continuous IV infusion.

Oral Dosing

Due to its rapid absorption and high lipophilicity, vinorelbine is ideally suited to oral administration. Studies have demonstrated a 28% bioavailability after administration of a liquid-filled gelatin capsule [37]. Using a dosage of 50 mg/m²/wk in 92 women over age 65, investigators confirmed a 32% first-line and 25% second-line response rate with oral therapy [37]. Vinorelbine given orally at 100 mg/m² is roughly equivalent to 30 mg/m² given intravenously, and the maximum tolerated oral dose has been established at 160 mg/wk, with a recommended dose of 80 mg/m²/wk suggested for future
phase II trials [38,39]. Oral vinorelbine has a similar side effects profile to weekly intravenous injections, with grade III or IV neutropenia still the predominant side effect, occurring in 43% to 63% of women [37,38]. Therefore, while the ease of administration may favor the use of oral vinorelbine, the IV route is still favored by the majority of investigators [40]. Furthermore, since weekly phlebotomy is still necessary to monitor patients for hematologic toxicity, this requirement may offset some of the advantages of oral dosing.

**Continuous Intravenous Infusion**

Other investigators believe that the most effective route of vinorelbine administration involves continuous intravenous infusion rather than bolus weekly dosing, because phase-specific agents are theoretically more active when tumors are continuously exposed to them. There is a long history of continuous-infusion research with vinca alkaloids, with 19 reports in the literature using this method of administration in breast cancer [41]. Researchers have recently proposed that vinorelbine has a better therapeutic index when administered over a longer period, or at least has the same therapeutic activity at a lower total dose. Toussaint et al published the results of a phase I/II trial in which 64 patients received vinorelbine as either first or second-line therapy [41]. The recommended dosage of 40 mg/m² was given every 21 days as an 8-mg/m² bolus followed by 8 mg/m²/d over 4 days. The overall response rate was 36%, with a median duration of response of 6 months. This continuous intravenous schedule was associated with equivalent hematologic toxicity but reduced neurotoxicity when compared to standard weekly bolus administration. Two additional side effects were more predominant with continuous dosing—peripheral asthenia and low-grade fever. Since no randomized trials have yet compared continuous-infusion to weekly intravenous therapy, further studies are needed to validate these preliminary results. Thus, at present, weekly bolus dosing remains the standard practice.

**Future Studies**

The precise role of vinorelbine in the treatment of breast cancer has yet to be determined. The unique pharmacokinetics, specific mechanism of action, and favorable side effects profile of this new agent have generated significant interest and enthusiasm. The initial European experience with vinorelbine as a first-line agent in metastatic breast cancer (producing response rates over 40%) has now been supported by US trials. These results have prompted further research into novel scheduling and new routes of administration. It remains to be seen whether vinorelbine will be best utilized as a single agent or as a component of combination therapy for metastatic disease. Current studies are attempting to answer this question. Growth factors have been utilized to overcome myelosuppression, thus permitting the development of new combination regimens with potentially higher response rates. In fact, a recent editorial has proposed a three-drug combination regimen using paclitaxel/Adriamycin/Navelbine (TAN), which may soon be tested in a clinical trial [40]. In addition, a multicenter US randomized trial comparing single-agent vinorelbine to paclitaxel as second-line therapy for metastatic breast cancer will begin later this year. This trial will use quality-of-life and resource-utilization outcomes analysis in an effort to determine whether single-agent vinorelbine offers unique advantages in palliative breast cancer treatment. Depending on the results of these and other studies, it is possible that vinorelbine may be incorporated into standard combination regimens, or perhaps even included in the adjuvant setting.

**References:**


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