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REVIEW

Safety and Efficacy of Vinorelbine in the Treatment of Non-Small Cell Lung Cancer

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Abstract: Lung cancer remains the most frequently diagnosed cancer in the United States, excluding non-melanoma skin cancer. Non-small cell lung cancer (NSCLC) constitutes the majority (more than 80%) of lung cancer diagnoses. Systemic therapy, with either cytotoxic chemotherapy and/or targeted therapies, has been established to provide benefit to patients with NSCLC in both the adjuvant and advanced disease settings. Vinorelbine, a semi-synthetic vinca-alkaloid has been extensively tested alone and in combination with other cytotoxic or targeted agents in the treatment of NSCLC. Its safety has been well established with neutropenia, anemia, nausea, and vomiting being the most frequently encountered toxicities. The data defining the risks and benefits of vinorelbine in the treatment of NSCLC will be summarized.

Keywords: vinorelbine, non-small cell lung cancer, chemotherapy, cetuximab, geriatrics

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Introduction

In the United States, lung cancer is the second most commonly diagnosed cancer in men and women, surpassed only by prostate cancer in men, and breast cancer in women. It remains the leading cause of death in either sex. It is estimated that 222,520 people (116,750 men and 105,770 women) will be diagnosed with, and 157,300 people will die of lung cancer in 2010.[1,2] More than 80% of lung cancer is the non-small cell type.[3]

The overall five-year survival of this disease is poor (less than 15%), related to the fact that 84% of patients are diagnosed at an advanced stage. Non-small cell lung cancer (NSCLC) is considered curable only when diagnosed prior to the development of metastasis and the 5-year overall survival is far better (86%) when the disease is diagnosed at the earliest stage. In total, 30% to 70% of patients who undergo resection will develop recurrence of the disease, which will be incurable for the vast majority. Thus, there is a need for effective adjuvant and palliative therapy for this disease.[2,4,5]

Platinum-based chemotherapy combinations have been demonstrated to provide a small, but significant overall survival (OS) advantage of 5% at 5 years in patients with completely resected NSCLC.[6] Vinorelbine is a vinca-alkaloid approved for the treatment of NSCLC, which also has demonstrated activity against breast and ovarian cancer. Vinorelbine has been evaluated in NSCLC in the adjuvant and advanced settings as a single agent and in combination with other agents (typically a platinum or gemcitabine) with modest success. In this article we will review the key clinical trials that have established the role of vinorelbine in the treatment of NSCLC.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Vinorelbine (5′nor-anhydro-vinblastine) is a semi-synthetic vinca-alkaloid that is manufactured from alkaloids extracted from the rosy periwinkle, Catharanthus roseus. It was first produced in 1979. Vinorelbine induces cytotoxicity by inhibiting the polymerization of tubulin dimers into microtubules, which in turn disrupts mitotic spindle formation and prevents cell division. This promotes apoptosis of cancer cells. Vinorelbine is selective for mitotic microtubules, with minimal activity on axonal or other microtubule classes. Therefore, it is less likely to produce neurotoxicity compared to non-selective microtubule inhibitors.[7–10]

Vinorelbine can be administered both orally and intravenously. The absolute bioavailability of oral vinorelbine is approximately 40%.[11] It is widely distributed in the liver, spleen, kidneys and lungs, and has slow efflux from tissue. The drug is highly bound to plasma protein (80%–90%) and its volume of distribution is approximately 25.4 to 40 L/Kg. It minimally crosses the blood brain barrier. The majority of vinorelbine metabolism occurs in the liver via the cytochrome P450, CYP3A4. The active metabolite of vinorelbine is deacetyl vinorelbine and the inactive metabolite is N-oxide vinorelbine. It is principally excreted by the liver via the biliary system (70%–80%); the urinary system accounts for the remainder (18%–20%). The half life is approximately 27.7 to 43.6 hours.[12–14]

The maximum tolerated dose (MTD) of vinorelbine was found to be 45 mg/m^2 in phase I trials. The major dose limiting toxicity is grade 3 leukocytopenia, which has an onset at day 8–10 after each dose. Through experience in phase II and III clinical trials, the optimal schedule of intravenous (IV) administration has been determined to be 25–30 mg/m^2 on days 1 and 8 of a 21 day cycle. There is insufficient data on the dosing of vinorelbine in patients with severe hepatic impairment, but it is recommended to reduce the dose based on the bilirubin level. Recommended dose adjustments for neutropenia are listed in Table 1. Dose reductions are not necessary in elderly patients, in the absence of hepatic dysfunction or hematologic toxicity.[14–17]

Extravasations injuries can be reduced with careful administration via central access and/or through use of a shortened duration of administration. Intravenous

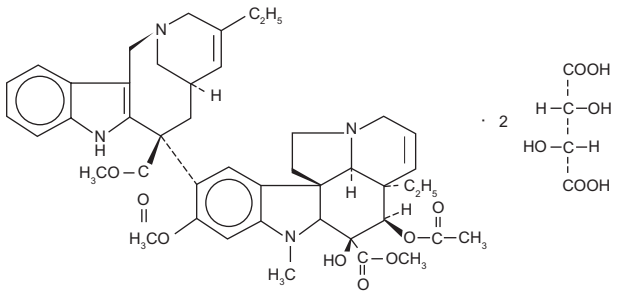

Figure 1. Chemical structure of vinorelbine tartrate (trade name, Navelbine®).[14]

Table 1. Recommended dose adjustments of vinorelbine.[15–18]

Hepatic impairment	**Serum bilirubin ≤2 mg/dL:** Recommended dose: 100%	**Serum bilirubin 2.1–3 mg/dL:** Recommended dose: 50%	**Serum bilirubin >3 mg/dL:** Recommended dose: 25%
Absolute Neutrophil Counts (ANC) on day of treatment	**ANC 1500 cells/mm3** Recommended dose: 100% of starting dose	**ANC 1000–1499 cells/mm³** Recommended dose: 50% of starting dose.	**ANC 1000 cells/mm³** a. Hold and repeat cell count every week. b. If 3 consecutive ANCs <1000 cells/mm³, discontinue vinorelbine.
Neutropenic fever while on treatment or 2 consecutive weekly doses held because of neutropenia:	75% of starting dose for ANC ≥1500 cells/mm³	37.5% of starting dose for ANC 1000–1499 cells/mm³	
Neurotoxicity ≥grade 2: Discontinue treatment.			
Dosage adjustment is not recommended for elderly patients in the absence of hepatic dysfunction or hematologic toxicity.			
Dosage adjustment is not necessary for patients with renal impairment.			

doses should be followed by at least 75–525 cc of normal saline or dextrose 5% water to reduce the incidence of phlebitis and inflammation.[18]

Vinorelbine in Adjuvant Therapy

In 1995, a landmark meta-analysis was published by the Non-small Cell Lung Cancer Collaborative Group, suggesting that treatment with platinum-based chemotherapy following complete resection of Stage I–III NSCLC provides a small, but significant survival advantage over best supportive care (BSC); the standard at that time.[7] These data prompted investigators to conduct several prospective, randomized trials aimed at confirming these results. Vinorelbine with cisplatin (VC) was a doublet studied in most of these trials.

Two large trials that examined multiple platinum containing chemotherapy doublets in the adjuvant setting, including the VC regimen, were the International Adjuvant Lung Cancer Trial (IALT) and the Big Lung Trial. The IALT was designed to evaluate the effect of cisplatin-based adjuvant chemotherapy on survival after complete resection of NSCLC. This was a large randomized trial involving a total of 1,867 patients who received cisplatin (80–120 mg/m^2) combined with each institution's choice of either etoposide or a vinca-alkaloid (56.6% received etoposide, 26.8% received vinorelbine, 11% received vinblastine, and 5.8% received vindesine). After a median follow-up of 56 months, patients assigned to receive chemotherapy had a significantly higher survival rate than those assigned to observation (44.5% vs. 40.4% at five years; hazard ratio {HR} for death = 0.86; 95% confidence interval {CI} = 0.76 to 0.98; $P < 0.03$). The patients who were assigned to receive chemotherapy also had a significantly higher disease-free survival (DFS) rate than those assigned to observation (39.4% vs. 34.3% at five years; HR = 0.83; 95% CI = 0.74 to 0.94; $P < 0.003$). After a median follow-up of 90 months, the beneficial effects of adjuvant chemotherapy on overall survival persisted, but were no longer statistically significant (HR = 0.91; 95% CI = 0.81 to 1.02; $P = 0.10$). The DFS benefit remained significant (HR = 0.88; 95% CI = 0.78 to 0.98; $P = 0.02$). The analysis of non-lung cancer deaths for the study period showed a HR of 1.34 (95% CI = 0.99 to 1.81; $P = 0.06$) in favor of observation. Out of 851 patients who received chemotherapy, 7 patients (0.8%) died from a therapy-related toxicity. The major grade 4 adverse events were neutropenia, thrombocytopenia, and vomiting. The toxicities for the patients receiving vinorelbine were not reported separately.[19,20]

The Big Lung Trial was a large multicenter trial in which 725 patients with completely resected NSCLC were randomized to observation (n = 361) or cisplatin-based chemotherapy (n = 364). The permitted chemotherapy regimens were as follows: MIC (Day 1: cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, ifosfamide 3 g/m^2), MVP (Day 1: cisplatin 50 mg/m^2, mitomycin 6 mg/m^2, vinblastine 6 mg/m^2), NP (Day 1: cisplatin 80 mg/m^2, vindesine 3 mg/m^2; day 8: vindesine 3 mg/m^2), and VC (Day 1: cisplatin 80 mg/m^2 and vinorelbine 30 mg/m^2; day 8 vinorelbine 30 mg/m^2). Forty-three patients (22%) received the VC regimen.

The trial was terminated early because of slow accrual after enrolling 381 patients. It failed to show an overall survival benefit for chemotherapy (HR 1.02; 95% CI, 0.77 to 1.35; $P = 0.90$). Toxicities for the VC arm were not reported separately.[21]

The VC combination was chosen for study as the sole adjuvant therapy regimen in two additional large randomized trials: the National Cancer Institute of Canada Clinical Trials Group's (NCIC CTG) JBR.10 trial, and the Adjuvant Navelbine International Trial Association (ANITA) trial. In the JBR.10 trial, 482 patients with completely resected stage IB or stage II NSCLC underwent randomization to 4 cycles of vinorelbine (25 mg/m^2 weekly) plus cisplatin (50 mg/m^2 on days 1 and 8, every 4 weeks) or observation. Forty-five percent of the patients had pathological stage IB disease and 55 percent had stage II. All patients had an ECOG performance status of 0 or 1. The JBR.10 trial demonstrated an 11% absolute improvement in overall survival at 5 years in favor of the chemotherapy combination (HR = 0.78; 95% CI, 0.61 to 0.99; $P = 0.04$). The subset analysis by stage showed a significant benefit for stage II patients (HR = 0.68; 95% CI, 0.50 to 0.92; $P = 0.01$), but not for patients with Stage IB disease (HR = 1.03; 95% CI, 0.70 to 1.52; $P = 0.87$). At a median follow-up of 9.3 years, the benefit for adjuvant chemotherapy remained (HR = 0.78; 95% CI, 0.61 to 0.99; $P = 0.04$). The most frequent grade 3 and 4 toxicities are listed in Table 2. There were two treatment related deaths; one from neutropenic sepsis and one from interstitial lung disease.[22]

The ANITA trial was a randomized, phase III study of patients with completely resected stage IB, II, and IIIA NSCLC. Eight hundred forty patients with stage IB-IIIA NSCLC from 101 centers in 14 countries were randomly assigned to observation (n = 433) or to chemotherapy (n = 407) with vinorelbine (30 mg/m^2 weekly) plus cisplatin (100 mg/m^2 every 4 weeks). After a median follow-up of 76 months (range 43–116), the median survival was 65.7 months (95% CI = 47.9–88.5) in the chemotherapy group and 43.7 months (95% CI = 35.7–52.3) in the observation group. The adjusted risk for death was significantly reduced in the patients assigned to chemotherapy compared to the controls (HR = 0.80, 95% CI = 0.66–0.96; $P = 0.017$). The overall survival at 5 years in the chemotherapy group was improved by 8.6%. In a subsequent follow-up, the 7 year OS benefit was

Table 2. Most frequent grade 3 and/or 4 toxicity for cisplatin and vinorelbine in the adjuvant setting (%).

Trial	Death from toxic effect	Neutropenia	Febrile neutropenia	Anemia	Thrombocytopenia	Infection	Asthenia	Neuropathy	Nausea/ vomiting[a]
JBR.10[23]	0.8	73	7	7	1	1	15	5	10
ANITA[24]	2	85	9	14	3	11	28	3	27

Note: [a]When nausea and vomiting were reported separately, the maximum number is shown.

Table 3. Clinical trials of vinorelbine in adjuvant therapy for NSCLC.

Trial name	N	Chemotherapy	Radiotherapy after chemotherapy	Median follow-up	OS HR (95% CI)	DFS HR (95% CI)
IALT[20]	1867	3 cycles, cisplatin 100 or 120 mg/m^2 Q4wks, or 4 cycles, cisplatin 80 mg/m^2 Q3wks, or 4 cycles, cisplatin 50 mg/m^2 d1 and 8 Q4wks Plus one of the following until the completion of cisplatin Vindesine 3 mg/m^2/wk $\times$ 4 then Q2wks, or Vinblastine 4 mg/m^2/wk $\times$ 4, then Q2wks, or Vinorelbine 25–30 mg/m^2 QW, or Etoposide 100 mg/m^2 d1–3 Q3–4wks	Optional	56 mos	0.86 (0.76 to 0.98) $P < 0.03$	0.83 (0.74 to 0.47) $P < 0.003$
Big Lung Trial[22]	725	3 cycles, cisplatin 80 mg/m^2 (doublets) or 50 mg/m^2 (triplets) all given Q21 days Plus one of the following until the completion of cisplatin (all are Q21 days) Vindesine 3 mg/m^2 on days 1 and 8, or Vinorelbine 30 mg/m^2 on days 1 and 8, or Mitomycin 6 mg/m^2 and ifosfamide 3 g/m^2, or Mitomycin 6 mg/m^2 and vinblastine 6 mg/m^2	Optional	23 mos	0.77 (0.66 to 0.89) $P = 0.0006$	0.97 (0.74–1.26) $P = 0.81$
JBR10[23]	482	4 cycles, cisplatin 50 mg/m^2 on days 1 and 8 Q28 days Vinorelbine 25 mg/m^2/wk $\times$ 16	None	60 mos	0.78 (0.61 to 0.99) $P = 0.04$	0.60 (0.45 to 0.79) $P < 0.001$
ANITA[24]	840	4 cycles, cisplatin 100 mg/m^2 Q28 days Vinorelbine 30 mg/m^2/wk $\times$ 16	Optional	76 mos	0.80 (0.66 to 0.96) $P = 0.017$	0.76 (0.64 to 0.91) $P = 0.002$

maintained at 8.4%. There were seven (2%) treatment related deaths. Frequencies of grade 3 or higher toxicities are listed in Table 2. The most frequent hematologic complications were neutropenia, anemia, and febrile neutropenia.

The Lung Adjuvant Cisplatin Evaluation (LACE) meta-analysis analyzed data from the 5 largest clinical trials of adjuvant cisplatin-based chemotherapy in NSCLC conducted since the 1995 NSCLC meta-analysis. This included the 4 trials described above, and one that did not incorporate vinorelbine. Data on 4,584 patients were examined with a median follow-up of 5.2 years (range per trial, 4.7 to 5.9 years). 1888 patients (41%) received the VC combination. There was a statistically significant OS benefit for adjuvant chemotherapy (HR = 0.89; 95% CI, 0.82 to 0.96; $P = 0.005$), corresponding to a 5-year absolute benefit of 5.4%, consistent with the results of the 1995 meta-analysis.[23] A prespecified subgroup analysis of the VC regimen was subsequently reported. The authors found that the OS benefit of adjuvant chemotherapy was significantly greater (P value for the interaction = 0.04) for the subgroup of patients who were randomized to VC vs. observation (HR 0.80, 95% CI: 0.70–0.91, $P < 0.001$) than for the subgroup of patients randomized to other chemotherapy regimens vs. observation (HR 0.95, 95% CI: 0.86–1.05, $P = 0.33$). The 5-year absolute OS benefit from adjuvant chemotherapy was 8.9% in the VC subgroup (55.1% vs. 46.2%). This suggestion that the VC regimen is superior to other adjuvant chemotherapy regimens previously evaluated supports its current use as a standard option for adjuvant therapy for NSCLC.[24]

As use of the VC regimen has become widely adopted in the adjuvant setting, more patients are being placed at risk of its potential late toxicities. Although there were no secondary malignancies reported in the above trials, one case of therapy-related acute myelogenous leukemia with a MLL gene rearrangement, t(11;19) (q23; p13.3) presenting 13 months after completion of 4 cycles of VC has been reported.[25]

Vinorelbine in Combination with Radiation Therapy for Locally Advanced, Unresectable Disease

Dual modality therapy combining chemotherapy with radiation therapy is a potentially curative therapy for unresectable, stage III or less NSCLC. Vinorelbine is not a standard in this setting in the United States, but its use as a radiation sensitizing agent has been examined in Japan.

Use of VC with thoracic radiation was determined to be safe in a phase I trial conducted by Sekine and colleagues. Eighteen patients with unresectable stage III NSCLC received the combination of cisplatin (80 mg/m^2) on day 1 and vinorelbine (20 mg/m^2 in level 1, and 25 mg/m^2 in level 2) on days 1 and 8 every 4 weeks for four cycles along with concurrent thoracic radiation to a total dose of 60 Gy. As a caveat, the radiation was delivered in 2 Gy fractions once daily for 3 weeks followed by a rest of 4 days. It was then resumed for an additional 3 weeks. The most common grade 3–4 toxicities were neutropenia (77% for level one; 100% for level two), infection (31% for level one; 60% for level two), and anemia (23% for level 1, 20% for level 2). Dose-limiting toxicity was noted in 33% of the patients in level one and in 60% of the patients in level two.[26]

Based on these results, a phase II study of this regimen was conducted in Japan with use of a modified cisplatin dosing regimen. Twenty-six patients with unresectable stage III NSCLC were treated with cisplatin (40 mg/m^2) and vinorelbine (20 mg/m^2) on days 1 and 8 of a 4 week cycle for a total of 2 to 4 cycles. The concurrent radiation started on day 2 of the first chemotherapy cycle and was delivered at 2 Gy per fraction to a total dose of 60 Gy over 6 weeks. After a median follow-up of 14 months, the overall response rate was 80.8% (95% CI, 60.6%–93.4%), with 5 (19.2%) complete responses. The median survival time was found to be 23 months (range, 4–43 months) and overall survival rate at 1 and 2 years were 80% and 56%, respectively. The most common grade 3–4 toxicities were neutropenia (84.6%), anemia (61.5%), infection (26.9%), esophagitis (7.7%), and pneumonitis (7.7%). There were no treatment related deaths.[27]

The efficacy of the cisplatin and vinorelbine combination with concurrent radiation for NSCLC has yet to be examined in a large, randomized clinical trial. The off-label use of this regimen cannot be recommended based on available data.

Vinorelbine in the Treatment of Advanced or Metastatic NSCLC

The landmark meta-analysis of data from 53 randomized trials published in 1995 by the NSCLC

collaborative group indicated a survival benefit for chemotherapy in advanced NSCLC (patients who have metastatic or recurrent disease or a malignant pleural effusion). It demonstrated an absolute 1-year survival benefit of 10% and a modest improvement in median survival of 1.5 months for patients treated with cisplatin-containing regimens compared with best supportive care alone.[7] Since this publication, the current practice for treating patients with metastatic disease has changed dramatically with the addition of several new agents and the now standard use of histology in guiding therapy. In the United States, vinorelbine is rarely used in the first line setting, with the exception being its use in combination with cisplatin and cetuximab, the epidermal growth factor receptor (EGFR) antagonist, based on data that will described below.

Vinorelbine in the First-Line Setting for Advanced Disease

The vinorelbine and cisplatin (VC) combination was first established as an effective regimen in the advanced setting in 1994 after demonstrating superiority over a standard regimen at the time of cisplatin and vindesine. In a phase III trial, a total of 612 patients with advanced NSCLC were randomized to receive three different chemotherapeutic regimens: vinorelbine alone (V), VC (vinorelbine 30 mg/m^2 weekly and cisplatin 120 mg/m^2 on day 1 and 29 and then every 6 weeks), or vindesine and cisplatin. The VC regimen was statistically superior to both V alone and the vindesine combination for response rate (30% vs. 14% vs. 19%), as well as median survival (40 weeks vs. 31 weeks vs. 32 weeks).[28]

This led to the Southwest Oncology Group's trial comparing VC to the combination of carboplatin with paclitaxel (PC). Two-hundred and two patients with advanced disease were randomized to VC (vinorelbine 25 mg/m^2 weekly and cisplatin 100 mg/m^2 on day 1 every 28 days) or PC (paclitaxel 225 mg/m^2 and carboplatin AUC 6 every 21 days). VC was found to be not statistically different to PC in regards to response rate (28% vs. 25%), median survival (8 months in both arms), and 1-year survival rate (38% vs. 36%). Grade 3 and 4 neutropenia was more common in the VC arm (76% vs. 57%), as was grade 3 nausea (18% vs. 7%). Grade 3 sensory neuropathy was statistically higher in the PC arm (13% vs. 3%). There was no difference observed between the two arms in quality of life.[29]

A four-arm cooperative study in Japan confirmed similar efficacy between the PC and VC regimens in addition to demonstrating the non-inferiority of VC to two additional platinum based regimens. In this study, 602 patients with advanced disease were randomized to receive one of 4 platinum doublets: VC (vinorelbine 25 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 every 21 days), PC (paclitaxel 200 mg/m^2 and carboplatin at an AUC of 6 min Xmg/ml every 21 days), IC (irinotecan 60 mg/m^2 on days 1, 8, and 15 plus cisplatin 80 mg/m^2 on day 1 every 28 days), or GC (gemcitabine 1000 mg/m^2 on days 1 and 8 plus cisplatin 80 mg/m^2 on day 1 every 21 days). There were no statistically significant differences in response rate or overall survival between patients in the 4 groups. All four regimens were well tolerated, with the most common grade 3 or 4 toxicities encountered in the VC arm being neutropenia, (88%), leukocytopenia (67%; significantly worse than IC), anemia (30%), and anorexia (20%). The median survival in each group was as follows: 11.4 months for VC, 12.3 months for PC, 13.9 months for IC, and 14.0 months for GC.[30]

The Italian study by Gebbia et al. was designed to determine the optimal dosing of vinorelbine in the VC combination. In this trial 278 patients with advanced NSCLC were randomized to receive either arm A: vinorelbine 25 mg/m^2 on day 1, 8, and 15 with cisplatin 100 mg/m^2 on day 1 of a 28 day cycle or arm B: vinorelbine 30 mg/m^2 on day 1 and 8 with cisplatin 80 mg/m^2 on day 1 of a 21 day cycle. There were no differences between arm A and arm B in median time to progression (TTP) (4.5 vs. 4.6 months), overall response rate (ORR) (34% vs. 32%), or median OS (9.45 vs. 10 months). The incidence of severe neutropenia was significantly worse in Arm A (68% vs. 34%; $P = 0.0001$), as was the incidence of febrile neutropenia (12% vs. 5%; $P = 0.026$). Due to an increased rate of dose delays and omissions, the weekly regimen (arm A) resulted in a lower overall dose intensity of vinorelbine.[31]

The VC doublet, however, began to lose favor in the United States when the TAX 326 study group demonstrated its inferiority to the combination of cisplatin with the newer taxane, docetaxel. Twelve hundred and eighteen patients with advanced disease were

Table 4. Clinical trials of vinorelbine in the first line setting for advanced NSCLC

Trial	N	Chemotherapy	Response rate	Median survival (months)	Major toxicity (Grade 3 or higher)
Le Chevalier et al[28]	612	Vinorelbine (30 mg/m²/wk) + Cisplatin (120 mg/m² on day 1 and 29, then Q6wks) Vindesine + cisplatin Vinorelbine alone (30 mg/m²/wk)	VC: 30% VsC: 19% V: 14% $P < 0.001$ for VC vs. V	VC: 9.2 VsC: 7.3 V: 7.1 $P = 0.01$ for VC vs. V	VC: Neutropenia ($P < 0.001$) VsC: Neurotoxicity ($P < 0.004$)
Kelly et al[29]	202	Paclitaxel (225 mg/m²) + Carboplatin (AUC 6) on day 1 every 21 days Vinorelbine (25 mg/m²/wk) + cisplatin (100 mg/m² on day 1 every 28 days)	PC: 25% VC: 28% P = not significant (NS)	PC: 8 VC: 8 P = NS	Sensory Neuropathy: PC vs. VC: 13% vs. 3% ($P < 0.001$) Neutropenia: VC vs. PC: 76% vs. 57% ($P = 0.008$)
Ohe et al[30]	602	VC (vinorelbine 25 mg/m² on days 1 and 8 + cisplatin 80 mg/m² on day 1 every 21 days) PC (paclitaxel 200 mg/m² + carboplatin AUC 6 every 21 days) IC (irinotecan 60 mg/m² on days 1, 8, and 15 + cisplatin 80 mg/m² on day 1 every 28 days) GC (gemcitabine 1000 mg/m² on days 1 and 8 + cisplatin 80 mg/m² on day 1 every 21 days)	VC: 33.1% PC:32.4% IC:31.0% GC:30.1% P = NS	VC: 11.4 PC: 12.3 IC: 13.9 GC: 14 P = NS	Neutropenia: VC(88%), PC(88%), IC(84%), GC(63%) Leukocytopenia: VC(67%), PC(45%), IC(48%), GC(33%)
Gebbia et al[31]	278	A: vinorelbine (25 mg/m² on day 1, 8, and 15) + cisplatin (100 mg/m² on day 1 of a 28 day cycle). B: vinorelbine (30 mg/m² on day 1 and 8) + cisplatin (80 mg/m² on day 1 of a 21 day cycle).	A: 34% B: 32% P = NS	A: 9.45 B: 10 P = NS	Neutropenia: A vs. B = 68% vs. 34% $P = 0.0001$ Febrile Neutropenia: A vs. B = 12% vs. 5% $P = 0.026$
Fossella et al[32]	1218	VC (Vinorelbine 25 mg/m²/wk + cisplatin 100 mg/m² on day 1 every 28 days) DC (docetaxel 75 mg/m² every 21 days + cisplatin 75 mg/m² every 21 days) DCb (docetaxel 75 mg/m² every 21 days + carboplatin at an AUC of 6 every 3 weeks)	DC: 31.6% VC: 24.5% DCb: 23.9% $P = 0.029$ for DC vs. VC	DC: 11.3 VC: 10.1 $P = 0.44$ P = NS for VC vs. DCb	Leukocytopenia: DC(42.8%), VC(54.5%), DCb(49.5%) Neutropenia: DC(74.8%), VC(79%), DCb(74.4%) Anemia: DC(6.9%), VC(24%), DCb(10.5%) Nausea: DC(9.9%), VC(16.4%), DCb(6.2%) Vomiting: DC(7.9%), VC(16.2%), DCb(4.2%)

randomized to receive VC (vinorelbine 25 mg/m^2 weekly and cisplatin 100 mg/m^2 on day 1 every 28 days), docetaxel 75 mg/m^2 every 21 days with cisplatin 75 mg/m^2 every 21 days (DC), or docetaxel 75 mg/m^2 every 21 days with carboplatin at an AUC of 6 every 3 weeks (DCb). The patients who received DC had statistically superior outcomes in regards to median survival (11.3 months for DC vs. 10.1 months for VC; $P = 0.044$), ORR (31.6% vs. 24.5%; $P = 0.029$), and 2-year survival rate (21% vs. 14%). There were no differences, however, in these variables between the VC and DCb groups. The rates of grade 3 to 4 anemia (24% for VC vs. 10.5% for DCb vs. 6.9% for DC), nausea (16.4% for VC vs. 6.2% for DCb vs. 9.9% for DC), and vomiting (16.2% for VC vs. 4.2% for DCb vs. 7.9% for DC) were higher in the VC group compared to DCb or DC ($P < .01$), whereas rate of neutropenia, febrile neutropenia, thrombocytopenia, and infection were similar amongst the three groups. Finally, patients treated with either docetaxel regimen scored consistently higher on quality of life scores than the VC treated patients.[32]

Vinorelbine as Switch Maintenance Therapy for Advanced Disease

The use of maintenance therapy following 4–6 cycles of initial systemic therapy has emerged as a popular strategy for improving progression-free survival and perhaps overall survival in advanced NSCLC.[33–35] When the agent selected for maintenance therapy is one that the patient has not previously received, it is referred to as "switch maintenance" therapy. In theory, switch maintenance may delay disease progression without providing overlapping toxicity or cross-resistance with the agents used in the initial therapy. Vinorelbine was selected for study as maintenance therapy in one randomized trial due to its excellent tolerability with prolonged administration.

In this trial, patients with Stage IIIB or IV NSCLC were enrolled after responding to initial therapy with either 2 cycles of MIC (mitomycin, ifosfamide, and cisplatin) followed by radiation for IIIB patients or 4 cycles of MIC for patients with advanced disease. 181 out of 221 patients with advanced NSCLC who responded to initial therapy were then randomized to receive maintenance therapy with vinorelbine (25 mg/m^2 weekly for 6 months) or no further therapy. Vinorelbine was well tolerated with the most common grade 3–4 toxicities consisting of leukocytopenia (36%), anemia (10%), infection (6%), peripheral neuropathy (6%), and pulmonary toxicity (6%). There was, however, no benefit demonstrated in the vinorelbine maintenance arm in PFS, OS, or survival rates at 1 and 2 years.[36]

Subsequent and ongoing trials aimed at evaluating maintenance therapy in advanced NSCLC have since focused attention on newer agents in lieu of vinorelbine.

Vinorelbine in Elderly Patients with Advanced Disease

The median age at diagnosis for cancer of the lung and bronchus is 69 years of age, and more than one half of patients with lung cancer are older than 60 years at diagnosis. Thirty percent are 70 years or older.[1] Older patients often have multiple and frequently interacting co-morbidities that may decrease the tolerability of systemic therapies. Vinorelbine has been evaluated extensively in elderly patients as a single agent due to its favorable toxicity profile and until recently was a standard, front-line, agent in this patient population.

Vinorelbine was first shown to be an effective agent in this population in the Elderly Lung Cancer Vinorelbine Italian Study (ELVIS) trial. This was a phase III trial that randomized 191 patients over 70 years old with advanced NSCLC to receive BSC alone or BSC and vinorelbine 30 mg/m^2 on days 1 and 8, every 21 days for up to six cycles. The trial was terminated early because of slow accrual, and data for 161 patients were analyzed. The median survival was significantly better in the chemotherapy group (28 vs. 21 weeks; HR = 0.65, 95% CI 0.45–0.93; $P = 0.03$). The vinorelbine group also had a significantly superior one year survival rate (32% versus 14%; P value not reported). The quality of life analysis also favored the chemotherapy arm. The most common grade 3 or 4 adverse effects experienced in the chemotherapy group were neutropenia (10%), leukocytopenia (7%), and anemia (16%).[37]

Oral anti-epidermal growth factor receptor (EGFR) tyrosine kinase inhibitors (TKI's), such as erlotinib and gefitinib, are standard, well-tolerated agents in the second-line setting for advanced NSCLC. After demonstrating superiority over best supportive care in the elderly population, vinorelbine was compared to gefitinib with the hypothesis that the oral agent would be

Table 5. Phase III trials of vinorelbine as first-line therapy for elderly patients with NSCLC.

Trial	N	Chemotherapy	Response rate	Median survival	Toxicity (Grade 3 or higher)
ELVIS[37]	191	Vinorelbine (30 mg/m^2 days 1 and 8 Q21 days) + BSC vs. BSC alone	V: 19.7% BSC: not reported	V + BSC: 28 wks BSC: 21 wks $P = 0.03$	Neutropenia (10%) Leukocytopenia (7%) Anemia (16%)
INVITE[38]	196	Gefitinib (G) (250 mg/day) orally vs. Vinorelbine (30 mg/m^2 on days 1 and 8 every 3 weeks)	At 6 and 12 mos G: 49.2% and 33.9% V: 54% and 33.2% $P = NS$	G: 25 wks V: 35 wks $P = NS$	Neutropenia: G: 0%, V: 19.8% Febrile Neutropenia: G: 0%, V: 7.3% Fatigue: G: 0%, V: 7.3%
MILES[39]	698	VG (vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2) G (gemcitabine 1200 mg/m^2) V (vinorelbine 30 mg/m^2) all treatment were administered on days 1 and 8 Q21 days)	VG: 21% G: 16% V: 18% $P = NS$	VG: 30 wks G: 28 wks V: 36 wks $P = NS$	Neutropenia: VG(18%), G(8%), V(25%) Fatigue: VG(7%), G(6%), V(7%)
SICOG[40]	120	V (vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks) VG (gemcitabine 1200 mg/m^2 and vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks	V: 15% VG: 22% P = NS	V: 18 wks VG: 28 wks $P < 0.01$	Neutropenia: VG(38%), V(28%) Thrombocytopenia: VG(13%), V(8%) Emesis: VG(15%), V(8%)

as efficacious and less toxic, while improving quality of life. The INVITE trial was a phase II, open-label, parallel-group study that randomized 196 chemotherapy naïve, elderly (age > 70) patients with advanced NSCLC to gefitinib alone (250 mg/day) or vinorelbine (30 mg/m^2 on days 1 and 8 every 3 weeks). There was no difference in the two groups for PFS (HR = 1.19; 95% CI, 0.6 to 1.65) or OS (HR = 0.98; 95% CI, 0.66 to 1.47). ORR and disease control rates were also similar between the two arms. Overall, the gefitinib group had superior QOL rates (24.3% vs. 10.9%), and fewer treatment-related grade 3 or higher adverse events (12.8% vs. 41.7%).[38]

In the largest trial to examine vinorelbine in the treatment of elderly patients with advanced disease, vinorelbine was compared against and in combination with another well-tolerated to agent, gemcitabine. The Multi-center Italian Lung Cancer in the Elderly Study (MILES), an open-label phase III trial, randomized 698 elderly (70 years or above) with advanced NSCLC to receive V (vinorelbine 30 mg/m^2), G (gemcitabine 1200 mg/m^2), or VG (vinorelbine 25 mg/m^2 and gemcitabine 1000 mg/m^2). All treatments were given on days 1 and 8 every three weeks for a maximum of six cycles. Compared to the V and G alone arms, the VG combination did not improve overall survival. The HR for death for patients receiving VG compared to V was 1.17 (95% CI = 0.95 to 1.44); it was 1.06 (95% CI = 0.86 to 1.29) for the comparison of VG to G. Quality of life was similar across all three groups. The chemotherapy combination resulted in significantly more thrombocytopenia and abnormalities in liver function testing than V alone. It resulted in more neutropenia, vomiting, fatigue, extravasation sequelae, cardiac toxicity, and constipation than G alone.[39]

The Southern Italy Cooperative Oncology Group and Interregional Association for the Study of Lung Carcinoma-Italy (SCIOG) trial also examined the VG regimen vs. V alone in elderly patients. They conducted, a phase III trial, that randomized 120 elderly (70 years or more) patients with advanced NSCLC to receive V (vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks) or VG (gemcitabine 1200 mg/m^2 and vinorelbine 30 mg/m^2 on days 1 and 8 every 3 weeks) with the primary endpoints of overall survival and quality of life. The overall response rate was 22% for the combination group compared to 15% for V alone. The VG regimen resulted in a superior median survival (29 vs. 18 weeks, $P = < 0.01$) and overall survival at 1 year (30% vs. 13%; $P < 0.01$) than V alone. The chemotherapy combination was also associated with an increased probability of being alive without symptom deterioration at 6 months (43% vs. 22%; $P = 0.002$) and an improved quality of life compared to V alone. Grade 3 or 4 neutropenia and thrombocytopenia occurred in 38% and 13% of patients in the VG group, respectively, compared to 28% and 8% in the V alone group. Severe emesis was also higher in the VG group (15% vs. 8%).[40]

The use of single-agent vinorelbine as first line therapy for advanced disease in the elderly population is likely to fall out of favor, now, in light of recent data suggesting that it is inferior to the standard platinum doublet of carboplatin with paclitaxel (PC). At the 2010 American Society of Clinical Oncology's annual meeting, results were presented from the IFCT-0501 trial. In this trial, 451 patients aged 70 to 89 with advanced disease were randomized to therapy with a single chemotherapeutic agent (either vinorelbine 30 mg/m^2 or gemcitabine 1,150 mg/m^2 on days 1 and 8 every 21 days), or the PC combination (paclitaxel 90 mg/m^2 on days 1, 8, and 15 and carboplatin AUC 6 on day 1 every 4 weeks). All patients who discontinued study therapy due to progression or toxicity received erlotinib 150 mg orally daily. At the planned interim analysis the PC group had significantly superior median OS (10.4 vs. 6.2 months, $P = 0.0001$) and PFS (6.3 vs. 3.2 months, $P < 0.0001$) compared to the single-agent chemotherapy group. Grade 3 or 4 hematological toxicities were higher for the PC group (54.1% vs. 17.9%). The final response, survival, and toxicity data have yet to be presented.[41]

Vinorelbine in Combination with Epidermal Growth Factor Receptor (EGFR) Targeted Therapy in Advanced NSCLC

The use of epidermal growth factor receptor (EGFR) targeted therapy is highly effective in selected subsets of patients with advanced NSCLC, especially those with EGFR activating mutations.[42]

Attempts to add the oral anti-EGFR TKI, gefitinib to vinorelbine or the VC combination were unsuccessful in a phase I trial due to unacceptably high rates of myelosuppression and febrile neutropenia.[43]

Cetuximab, an anti-EGFR IgG-1 monoclonal antibody, was studied in addition to the VC regimen in the FLEX (First-Line ErbituX in lung cancer) trial. The FLEX trial was a large, phase III trial involving 1125 patients with EFGR-expressing (by immunohistochemistry), advanced NSCLC. Patients were randomly assigned to receive VC (vinorelbine 25 mg/m^2 on days 1 and 8 and cisplatin 80 mg/m^2 on day 1 every 3-weeks up to six cycles) or VC plus cetuximab (Cetuximab at 400 mg/m^2 on day 1, then 250 mg/m^2 weekly). Cetuximab was continued after the completion of chemotherapy until disease progression or the development of unacceptable toxicity. Patients who received VC with cetuximab had improved overall response rates (36% vs. 29%, P = 0.010) and survival (median OS 11.3 vs. 10.1 months; HR = 0.871; 95% CI, 0.762–0.996; P = 0.044) compared to VC alone. The benefit was seen in all histological subgroups. There was no difference, however, in median PFS (4.8 months for both groups). The incorporation of cetuximab was associated with significantly higher rates of Grade 3 or 4 leukocytopenia (25% vs. 19%), febrile neutropenia (22% vs. 15%), acne-like rash (10% vs.<1%), diarrhea (4–5% vs. 2–3%), and infusion-related reactions (3–4% vs. 1%).[44]

Although the cetuximab with VC regimen in EGFR expressing advanced NSCLC has been incorporated in current guidelines on the management of NSCLC[45] its use in the United States has been limited. The VC regimen has been questioned as an appropriate comparator arm due to its inferior results when compared to DC in the TAX 326 trial described previously. In support of this argument, the addition of cetuximab to the more commonly used PC regimen was unable to produce a significant survival benefit.[46] Furthermore, the cost-effectiveness of this regimen has been questioned. One analysis estimated the incremental cost effectiveness ratio for adding cetuximab to chemotherapy to be the equivalent of roughly 486,500 US dollars per quality-adjusted life year gained.[47]

Conclusion

Lung cancer remains the leading cause of cancer death in the United States. Its management is directed by the stage at presentation. For patients who are fortunate to undergo a complete resection, platinum-based adjuvant chemotherapy, has demonstrated a survival benefit. The combination of vinorelbine with cisplatin has the most robust data in this setting.

For patients with locally advanced, unresectable disease, dual modality therapy combining chemotherapy with radiotherapy remains the standard treatment. Experience with vinorelbine for this indication is limited and requires further investigation.

In patients who present with advanced or recurrent disease, vinorelbine in combination with cisplatin (VC) is an effective regimen. In light of data from the TAX 326 trial demonstrating inferiority of the VC regimen to the combination of cisplatin and docetaxel, however, its use has fallen out of favor.[33] In addition, vinorelbine has no demonstrated efficacy as a switch maintenance therapy for patients with advanced disease following a response to first-line therapy.

Lung cancer is a disease of advanced age with over 30% of the patients diagnosed after 70 years of age.[1] Vinorelbine has been shown to be an effective and well tolerated agent for elderly patients with advanced disease. Recently presented data, however, from the IFCT-0501 trial, suggest that the standard, chemotherapy combination of paclitaxel and carboplatin can be safely administered to this patient population in the first-line setting, with greater efficacy than vinorelbine alone.[42]

The benefit of EGFR targeted therapy in selected patients with advanced NSCLC, specifically those with tumors harboring an EGFR activating mutation, has been well established. Addition of the anti-EGFR monoclonal antibody, cetuximab, to the VC regimen results in a small, but significant survival benefit in patients with advanced disease as demonstrated in the FLEX trial.[45] This combination has been incorporated into current guidelines on the management of NSCLC, but its use has been controversial, due to potential limitations in the design of the FLEX trial, as well as questions about its cost-effectiveness.

The management of NSCLC is an ever evolving topic that has recently seen major advancements. As the treatment of all cancer becomes increasing targeted and personalized, the role of vinorelbine is likely to change. At this time, based on its tolerability and proven efficacy, vinorelbine remains a vital agent in the treatment of NSCLC.

Disclosure

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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