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Oral Vinorelbine in the Treatment of Non-Small Cell Lung Cancer

Rationale and Implications for Patient Management

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Abstract

Vinorelbine is an established treatment for advanced non-small cell lung cancer (NSCLC), both as a single agent and in combination chemotherapy. Recently, an oral form of this agent has been developed. Before accepting an established agent in a different administration form, rigorous testing is required to answer such questions as reliable bioavailability, continued safety and preservation of efficacy. In addition, an oral agent must provide patient convenience and acceptance, while being an economically sound approach.

Oral vinorelbine was found to have acceptable and reliable pharmacokinetic profiles at clinically relevant dosage levels. Oral vinorelbine was found to have approximately 40% bioavailability; thus, a dose of 80 mg/m^2 orally is the equivalent of 30 mg/m^2 intravenously, and 60 mg/m^2 orally is the equivalent of 25 mg/m^2 intravenously. Studies also concluded a lack of food effect on the administration of oral vinorelbine. In addition, no drug-drug interactions were found with a variety of commonly used antineoplastic agents.

Vinorelbine, either orally or intravenously, has been investigated in randomised phase II trials as a single agent and in combination with cisplatin or carboplatin in patients with NSCLC. In general, response and survival results with oral vinorelbine appeared similar to the intravenous agent. Adverse-effect profiles were also similar for the two formulations. Clearly, the issue of venous irritation does not exist with oral vinorelbine; however, nausea and vomiting were more frequent when vinorelbine was administered orally compared with intravenously when no planned antiemetic therapy is given.

Most chemotherapy drugs are given intravenously; however, the increasing availability of oral antineoplastic agents presents challenges and opportunities for both patients and physicians.

One issue is whether patients want oral chemotherapy as a clinical option. Two recent studies addressed this question.[1,2] In one survey, which included >100 patients, 89% expressed a preference

for oral over intravenous chemotherapy if the former produced equal or better efficacy.[1] A second report[2] involved 31 evaluable patients in a crossover trial, with patients randomised to receive oral UFT (the fluorouracil prodrug tegafur/uracil) or intravenous fluorouracil. In this study, >80% of patients expressed a preference for the oral treatment.

Another way to look at the issue of patient preference is to ask whether or not oral chemotherapy addresses major concerns that patients have in receiving chemotherapy. During the last two decades, several surveys have asked patients about their concerns. Table I lists ten of the top concerns (in alphabetical order) from two of these studies.[3,4] While considerable progress in supportive care has helped with some of these key issues (such as the control of emesis), it is clear that many aspects remain as serious now as when these surveys were first conducted. Of these ten concerns, nearly half (as indicated in the table) could potentially be lessened through the use of oral chemotherapy. Not only would obvious issues such as venipuncture be eliminated by using the oral route, but time spent in the clinic and the effect on the patient's family could both be markedly reduced by this simple advance. Successfully addressing these issues with oral treatment could effectively alter patients' often negative perceptions about cancer chemotherapy.

While these studies show that patients will accept effective oral chemotherapy and that such an approach addresses major patient-expressed needs, these surveys do not address other major treatment concerns of physicians. It goes without saying that an oral chemotherapy should be at least as safe and effective as its intravenous counterpart. Within the former consideration, would an oral agent introduce adverse effects (such as gastrointestinal toxicity) that are not seen for the intravenous agent? In addition, questions of reliable bioavailability, patient compliance and pharmacoeconomics would all need to be addressed.

Table I. Principal concerns in patients receiving intravenous chemotherapy (in alphabetical order)[3,4]

Alopecia
Dyspnoea, polyuria
Fatigue
Impact of treatment on family and work[a]
Insomnia, depression, anxiety
Nausea
Time at the clinic[a]
Venipuncture[a]
Vomiting

a Indicates patient concerns that would be addressed through the use of oral chemotherapy agents.

Intravenous vinorelbine has been used both as a single agent and in combination with cisplatin for the first-line treatment of unresectable, advanced non-small cell lung cancer (NSCLC) for over a decade. More recently, an oral formulation has been approved and is now commercially available for the treatment of NSCLC in 32 countries, including 17 countries in the EU; it is not yet commercially available in North America. This article reviews available clinical experience on the use of oral vinorelbine in the treatment of NSCLC. A comprehensive search through MEDLINE was conducted over the period from 1995 to May 2006. Reference lists of relevant articles were also searched.

1. Pharmacological Considerations

Concerns have been raised with the use of older antineoplastic agents that have oral forms (e.g. etoposide, methotrexate) because of a lack of confidence in the pharmacokinetic profiles of these drugs. For example, oral methotrexate can have variable absorption (20–90%), even in the same individual receiving a different course of treatment. Additionally, the low bioavailability in commonly used oncological dose ranges of both etoposide (at 100 mg/m^2) and methotrexate (at doses >30 mg/m^2) has limited confidence in their use.[5,6]

Currently, two newer antineoplastic agents, vinorelbine and capecitabine, are available for use in oral treatment schedules in many countries and have been investigated in various patient groups.[7-11] Results for these two compounds revealed reliable oral bioavailability (capecitabine 61%; oral vinorelbine approximately 40%), and similar pharmacokinetic and pharmacodynamic profiles when compared with those documented for corresponding injectable

compounds (fluorouracil and injectable vinorelbine, respectively).

Pharmacokinetic studies indicate that the maximal concentration obtained with oral vinorelbine is less than that obtained with the intravenous formulation, but the total patient exposure, as expressed in the area under the curve (AUC), is comparable (figure 1).[12] Oral vinorelbine doses of 60 and 80 mg/m^2 were shown to be bioequivalent to intravenous doses of 25 and 30 mg/m^2, respectively.[13] Additionally, concomitant food ingestion had no effect on the pharmacokinetics of oral vinorelbine in a study of fasted (n = 6) versus fed (n = 6) patients with solid tumours or lymphomas.[14]

An issue with oral chemotherapy (but not with intravenous therapy) is the problem of a patient vomiting within 2–3 hours of drug administration and whether re-administration is needed. A pharmacokinetic modelling study examined this question and showed that early vomiting following oral vinorelbine had no effect on the absolute bioavailability of vinorelbine. This study indicates that absorption of the oral vinorelbine is very rapid (occurring in <20 minutes) and is largely complete far earlier than the onset of chemotherapy-induced emesis, which generally requires 1–2 hours.[12]

Age does not influence the clearance of oral vinorelbine,[15] and vinorelbine has no significant drug interactions with cisplatin, docetaxel, paclitaxel, capecitabine, gemcitabine or cyclophosphamide.[16,17] These pharmacokinetic results establish the basis for accepting the clinical equivalence of oral vinorelbine with the intravenous formulation.

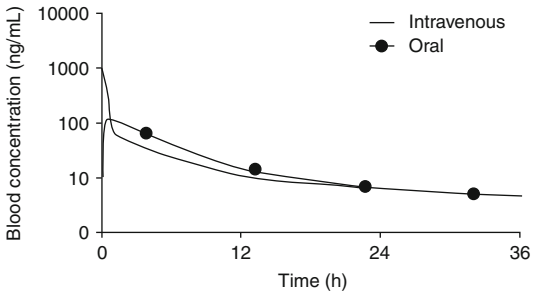

Fig. 1. Mean blood pharmacokinetic profile observed after administration of 30 mg/m^2 intravenous or 80mg/m^2 oral vinorelbine in phase I patients (reproduced from Variol et al.,[12] with permission).

With this scientific underpinning, it becomes reasonable to evaluate comparative oral and intravenous trials for efficacy and adverse effect results.

2. Oral Vinorelbine as Single-Agent Therapy in Non-Small Cell Lung Cancer

Table II summarises the results from prospective randomised trials comparing single-agent therapy with best supportive care (BSC), or placebo with or without BSC, in NSCLC.[18-23] Survival benefits have only been shown for four single agents: vinorelbine, paclitaxel, docetaxel and erlotinib. A large randomised trial with gemcitabine did not demonstrate a survival advantage for that agent when compared with BSC.[18] Similarly, no advantage was seen with gefitinib compared with placebo plus BSC.[22]

The positive comparative results for vinorelbine versus BSC were shown with the intravenous formulation.[19] This benefit, together with the comparative pharmacokinetic data for the oral form, prompted a comparative study between the two formulations. In a randomised phase II trial, 115 patients with stage IIIB or IV NSCLC (performance status [PS] 0–1, and no previous chemotherapy for metastatic disease) were assigned to intravenous vinorelbine (30 mg/m^2/week) or to oral vinorelbine (60 mg/m^2/week, first three doses, followed by subsequent doses of 80 mg/m^2/week).[24] Efficacy data were similar for the two treatment groups. The overall major response rate was 12% and 11% with the oral and intravenous formulations, respectively, the median survival time was 9.3 versus 7.9 months, and the 1-year survival rates were 41% versus 29%.

This trial also allowed an analysis of the comparative toxicities of the two routes of administration. Grade 3–4 neutropenia, the main haematological toxicity of vinorelbine, was observed in 25% of cycles in the intravenous group and in 7% of those randomised to the oral formulation, based on the dose administration schedule outlined above. No major differences between the two groups were found with other haematological toxicities (thrombocytopenia, anaemia and febrile neutropenia). As for non-haematological toxicities, emesis was more

Table II. Results from prospective, randomised trials involving comparison of single agents with best supportive care (BSC) or placebo ± BSC in patients with advanced non-small cell lung cancer

Study	Regimen	No. of patients	Major response rate (%)	Median survival (mo)	1-year survival (%)
Gridelli[19]	Vinorelbine	76	20	6.5*	32
	BSC	78		4.9	14
Ranson et al.[20]	Paclitaxel	79	16	6.8*	35
	BSC	78		4.8	28
Roszkowski et al.[21]	Docetaxel	137	13	6.0*	25
	BSC	70		5.7	16
Anderson et al.[18]	Gemcitabine	150	19	5.7	25
	BSC	150		5.9	22
Thatcher et al.[22]	Gefitinib	1126	8.0†	5.6	27
	Placebo + BSC	562	1.3	5.1	21
Shepherd et al.[23]	Erlotinib	488	8.9†	6.7†	31
	Placebo	243	<1.0	4.7	22

* $p < 0.05$ vs BSC; † $p < 0.001$ vs placebo.

common with the oral than the intravenous formulation (11% vs 0% of cycles), as was nausea and vomiting (8% vs 3%). However, in this specific study, patients did not routinely receive antiemetic therapy. As antiemetic guidelines recommend preventive treatment for patients receiving chemotherapy with a ≥10% risk of emesis, prophylactic use of an antiemetic would be expected to reduce the emetic risk.[10,25]

Another trial was conducted as a single-arm, phase II study, specifically in elderly patients (aged 70–82 years) with NSCLC. These patients were given oral vinorelbine 60 mg/m^2/week for the first 3 weeks and 80 mg/m^2/week thereafter.[10] Grade 3–4 neutropenia was noted in 30.8% of treatment cycles and grade 3–4 leukopenia in 21.5%. Nausea and diarrhoea were generally mild or moderate (grade 3 only) and were experienced by 3.6% and 5.4% of patients, respectively. This favourable tolerability profile permitted an increase in oral vinorelbine dosage from 60 to 80 mg/m^2 in two-thirds of the patients. Moreover, efficacy data were in line with those already observed in the younger population treated with the same oral vinorelbine schedule.[24] The objective response rate was 12.8%, the median duration of response was 5.2 months, and median survival was 8.2 months.[10] These findings support, in the clinical practice setting, data from prior studies showing that the pharmacokinetic behaviour of orally administered vinorelbine is not influenced by age.

3. Vinorelbine in Platinum-Based Doublets

Platinum-based doublets induce the highest response rate and median survival in patients with advanced NSCLC; therefore, they are considered the standard treatment for this disease.[26,27] Intravenous vinorelbine has been widely used in such doublets and is currently considered a standard in combination with cisplatin.

The most common major toxicity of combination chemotherapy for lung cancer is neutropenia. This is clearly a consideration for the classical cisplatin plus vinorelbine regimen in which cisplatin is given once every 4 weeks and vinorelbine is administered weekly. A recent prospective randomised study compared the classical weekly vinorelbine (plus cisplatin every 4 weeks) regimen with a combination of vinorelbine given on days 1 and 8 plus weekly cisplatin on a 3-week cycle.[28] This study indicated that the day 1 and day 8 vinorelbine regimen with weekly cisplatin allows a dose intensity >90%, with a comparable degree of efficacy but a significantly lower toxicity.

On the basis of the comparative single-agent studies showing similar results between oral and intravenous single-agent vinorelbine, trials involv-

ing a combination of cisplatin and oral vinorelbine have now been conducted. Two such studies have recently been published. The first study[29] involved the use of alternating intravenous vinorelbine (25 mg/m^2 on day 1) and oral vinorelbine (60 mg/m^2 on days 8, 15 and 22) in combination with cisplatin (100 mg/m^2 on day 1) in 4-week cycles (table III). The second study,[30] outlined in table IV, evaluated 3-week cycles of exclusively oral vinorelbine (60 mg/m^2 in the first cycle [80 mg/m^2 in subsequent cycles] on days 1 and 8) combined with cisplatin (80 mg/m^2 on day 1). The results reported were similar to those observed with the classical intravenous vinorelbine in combination with cisplatin, except that the oral vinorelbine schedule[30] was associated with a lower incidence of haematological toxicity than both its intravenous counterpart[28] and the alternating intravenous-oral therapy;[29] grade 3–4 neutropenia was seen in 29.1% of the patients in the oral vinorelbine study versus 40–75% in the intravenous vinorelbine study and 73% in the oral plus intravenous vinorelbine study (tables III–IV). Results of the symptom scores for patients given oral vinorelbine and cisplatin also showed favourable outcomes; symptoms followed included chest pain, cough, haemoptysis and dyspnoea, with the mean weight remaining stable throughout the study period.[30]

Table III. Phase II study of alternating oral and intravenous vinorelbine plus cisplatin in 56 patients with non-small cell lung cancer[29] a

Parameter	Result
Efficacy (n = 51 evaluable patients)	
Objective response	33% of patients
Stable disease	45% of patients
Progression-free survival	5.5mo
Median survival	8.9mo
Tolerability (grade 3–4 WHO)	
Neutropenia	73% of patients
Anaemia	12% of patients
Nausea/vomiting	9% of patients

a Median age of patients was 60 years (range 40–74 years). Patients received intravenous vinorelbine 25 mg/m^2 on day 1, oral vinorelbine 60 mg/m^2 on days 8, 15 and 22, and cisplatin 100 mg/m^2 on day 1, every 4 weeks.

Table IV. Phase II study of oral vinorelbine only plus cisplatin in patients with non-small cell lung cancer[30] a

Parameter	Result
Efficacy (n = 49 evaluable patients)	
Objective response	26.5% of patients
Median survival	10mo
1-year survival	43% of patients
Tolerability (n = 56 evaluable patients)	
Neutropenia (grade 3–4 NCI-CTC)	32.6% of patients
Anaemia	58.2% of patients

a Patients received oral vinorelbine 60 mg/m^2 on days 1 and 8 on the first cycle and then 80 mg/m^2 on days 1 and 8 from the second cycle plus cisplatin 80 mg/m^2 on day 1, every 3 weeks.

NCI-CTC = National Cancer Institute of Canada Common Toxicity Criteria.

As an alternative to cisplatin, carboplatin is often used in the metastatic setting in many countries. In phase II–III studies of intravenous vinorelbine plus carboplatin (the latter used at a dose of AUC = 5) in a total of >500 patients, response rates varied from 20–45% and median survival varied from 5.6–12.3 months.[31-33] A phase II study evaluated the role of oral vinorelbine in combination with carboplatin in 44 patients with stage IIIB or IV NSCLC.[11] The dose-administration schedules in this study were (for a 3-week cycle): carboplatin (AUC 5) on day 1 plus intravenous vinorelbine 25 mg/m^2 on day 1 and oral vinorelbine 60 mg/m^2 on day 8 or 15. This treatment yielded an overall response rate of 18%, a median duration of response of 7.9 months, median progression-free survival of 5.1 months, median survival of 9.3 months and a 1-year survival rate of 42%. Grade 3–4 neutropenia was noted in 39% of cycles; mild (≤grade 2) thrombocytopenia occurred in 29%, and febrile neutropenia or neutropenic infections occurred in <1% of patients. A quality-of-life (QOL) questionnaire carried out at baseline and after 3 months of treatment showed no marked deterioration in functional or symptom scores. The authors concluded that alternating intravenous and oral vinorelbine plus carboplatin is an active regimen in NSCLC.

Further well designed studies of oral vinorelbine plus platinum-based schedules are warranted to

evaluate longer courses of vinorelbine treatment or maintenance regimens in initial treatment responders, and also to evaluate such schedules in elderly patients to determine how long and how intensively such patients should be treated.

4. Vinorelbine Plus Cisplatin in Chemoradiation

In the treatment of locally advanced NSCLC, radiotherapy plus cisplatin-based chemotherapy is superior to radiotherapy alone, and reduces the relative risk of death by about 13%.[34] Moreover, concurrent chemo/radiotherapy is superior to sequential regimens in some trials,[35] while other studies do not demonstrate significant differences. Several options exist when combining radiotherapy with chemotherapy: (i) induction chemotherapy, followed by radiotherapy; (ii) simultaneous radiotherapy plus chemotherapy; (iii) induction chemotherapy, followed by concurrent radiotherapy and chemotherapy; and (iv) concurrent radiotherapy with chemotherapy, followed by consolidation chemotherapy.

Historically, the most frequently used option until 1992 was induction chemotherapy followed by radiotherapy. In that year, evidence from the European Organisation for Research and Treatment of Cancer showed a survival advantage for the simultaneous administration of radiotherapy with daily cisplatin.[36] A large randomised phase II trial of cisplatin plus vinorelbine, paclitaxel or gemcitabine, with each regimen being followed by concomitant chemotherapy and radiotherapy, showed that these schedules had similar efficacy: response rates ranged from 67% to 74%, and 1-year survival rates were from 62% to 68%.[37] However, the safety of the schedules was markedly different: the toxicity of the cisplatin plus vinorelbine combination was observed to be significantly less than with the other two combinations.

The combination of oral vinorelbine plus cisplatin in a schedule of induction chemotherapy followed by concurrent chemoradiation was studied in 56 patients with stage III NSCLC.[38] The response rate was 37% after induction chemotherapy, and 56% following concomitant chemotherapy and radiotherapy, indicating that oral vinorelbine plus cisplatin yields a response rate similar to that reported with intravenous vinorelbine plus cisplatin. To answer the question of whether adding consolidation chemotherapy is beneficial following concurrent chemotherapy and radiotherapy, a phase I study of oral vinorelbine 40–60 mg/m^2 and fractionated doses of cisplatin in combination with standard radiotherapy has been completed.[39]

5. Conclusion

Several clinical trials in patients with advanced NSCLC have shown that oral vinorelbine has a similar pharmacokinetic profile resulting in comparable efficacy with the intravenous formulation. Additionally, vinorelbine given on days 1 and 8 of a 3-week cycle along with cisplatin on day 1 is well tolerated and may be a more desirable schedule than the classical vinorelbine plus cisplatin regimen.

The oral form also plays an important role in the treatment of advanced NSCLC when used in platinum-based doublets. Having an oral dosage formulation of vinorelbine presents many opportunities for using this agent with either concurrent or sequential radiotherapy. The pharmacokinetic and recent clinical studies suggest that oral vinorelbine may be particularly interesting to investigate in the adjuvant setting.

These issues are the subject of ongoing investigations. Clearly, oral chemotherapy can affect many aspects of cancer care. The oral form presents many opportunities to simplify treatment for patients, to improve outcomes, and to change the perception of chemotherapy for patients and families.

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