

Oral vinorelbine: a feasible and safe partner for radiotherapy in the treatment of locally advanced non-small cell lung cancer

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Background: Concurrent chemoradiotherapy (CCRT) using cisplatin-based doublets represents the standard of care for locally advanced non-small cell lung cancer (NSCLC), having shown good efficacy and activity in clinical trials. Locally advanced NSCLC occurs frequently in the elderly population, which is often excluded by platinum-based CCRT administration, due to severe associated toxicities. This limitation has been overcome using new-generation drugs such as gemcitabine, docetaxel, paclitaxel, and vinorelbine, which have shown not only to be efficacious but also to have a favorable toxicity spectrum, both in association with cisplatin and as single agents. Vinorelbine is a vinca alkaloid that binds to tubulin, thus inhibiting mitotic microtubule polymerization. Previous studies have clearly demonstrated that vinorelbine acts as a radiosensitizing agent when administered intravenously or orally. Moreover, oral administration of vinorelbine has shown a good clinical safety profile in both elderly and younger patients.

Methods: A comprehensive review of the literature data regarding use of oral vinorelbine concurrently with radiotherapy in NSCLC was done.

Conclusion: Single-agent oral vinorelbine may represent an effective therapy option for elderly patients with locally advanced lung cancer. This review has described the use of oral vinorelbine both as a monochemotherapy and in combination with cisplatin in the context of CCRT.

Keywords: locally advanced NSCLC, chemoradiotherapy, oral vinorelbine

Background

Lung cancer causes ~1.3 million deaths annually, and ~45% of patients are diagnosed with locally advanced stage of the disease. The standard treatment for locally advanced non-small cell lung cancer (NSCLC) is concurrent chemoradiotherapy (CCRT), using cisplatin-based doublets;¹ nevertheless, severe toxicity is often expected, especially in elderly patients, which represents ~30% of all NSCLC. To avoid this issue, more active and better tolerated novel agents, which also act as radiation sensitizer, have been identified in clinical trials, namely docetaxel,² gemcitabine,³ and vinorelbine. Vinorelbine is a semisynthetic vinca alkaloid that binds to tubulin, thus inhibiting mitotic microtubule polymerization. Oral vinorelbine has shown a good clinical safety profile in both elderly and younger patients, without differences in absorption, blood concentrations, and absolute bioavailability. It has also shown a good safety profile, demonstrating to guarantee a good quality of life (QoL) in elderly patients.⁴

Pharmacokinetic–pharmacodynamic characteristics of oral vinorelbine formulation do not differ from those seen for the intravenous formulation, in both the younger and elderly patients.⁵ Oral vinorelbine is also better tolerated when compared to the

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intravenous formulation, due to the absence of infusion-related phlebitis and the possibility to avoid hospitalization for its administration.

In vitro studies carried out by Eldestein et al⁶ showed that vinorelbine has a radioenhancer cell cycle-dependent activity on tumor cells, exerting its widest efficacy in cell killing during the G2 phase. Fukuoka et al elucidated the cellular mechanism of radiosensitization using a clonogenic assay. They concluded that vinorelbine, used at a minimally toxic concentration, sensitizes human NSCLC to ionizing radiations, by favoring the accumulation of tumor cells in G2/M phase of the cell cycle, thus increasing susceptibility to apoptosis induction.⁷

The oral formulation is able to maintain the radiosensitization activity at low dose also, when compared with the intravenous formulation.

The literature reports few consistent studies on the use of oral vinorelbine as a single agent, with only few patients having been treated with the oral formulation, in the context of CCRT.

Interestingly, Ptaszek et al⁸ used oral vinorelbine in combination with cisplatin as a neoadjuvant regimen in locally advanced NSCLC, obtaining a fairly good, 40%, overall response rate (ORR), which led their patients to experience a less extensive surgery. This observation probably indicates the beneficial activity of the drug.

To define the role of oral vinorelbine, given concomitantly with radiotherapy in elderly patients with locally advanced NSCLC, the following topics were searched for in PubMed and Google Scholar: “Non small cells lung cancer, concurrent chemoradiotherapy, and oral vinorelbine.” Furthermore, several recent Phase I/II, II, and III studies assessing the safety and activity of oral vinorelbine administered concurrently with radiotherapy were identified.

Methods

Data regarding the use of oral vinorelbine, given concurrently with (chemo)radiotherapy, in patients diagnosed with locally advanced NSCLC were collected from PubMed. The following keywords were used: “Oral”; “Vinorelbine”; “NSCLC”; and “Locally advanced.” Articles published between the years 1996 and 2016 were chosen, and data from Phase I/II, II, and III trials were mainly retrieved.

Oral vinorelbine and cisplatin given concurrently with chest radiotherapy

In 2006, a Phase I trial was performed by Beckmann et al⁹ to establish the safety and correct dose of oral vinorelbine

in combination with cisplatin and concurrent chest radiotherapy.

Eleven patients with stage IIIB NSCLC were treated with radiotherapy at a total dose of 66 Gy concurrently with two cycles of cisplatin and oral vinorelbine administered at three different levels (40, 50, and 60 mg/m²) on days 1, 8, and 15 over 4 weeks. Cisplatin was given at 20 mg/m² on days 1–4. After CCRT, two cycles of adjuvant chemotherapy, using the same regimen, were administered.

Esophagitis was identified as the dose-limiting toxicity. Nine patients received adjuvant chemotherapy, and the most relevant described toxicities were G3 neutropenia, anemia, and thrombocytopenia, while the ORR was 73%.

The authors concluded that 40 mg/m² of oral vinorelbine was equivalent to 15 mg/m² of intravenous formulation, and they recommended oral vinorelbine 50 mg/m² (days 1, 8, and 15 over 4 weeks) in combination with cisplatin 20 mg/m² on days 1–4.

In 2008, Krzakowski et al¹⁰ performed a Phase II trial using oral vinorelbine and cisplatin as induction chemotherapy, followed by the same doublet given concurrently with chest radiotherapy until a total dose of 66 Gy. Primary end point was the percentage of objective response, and secondary end points were duration of response, progression-free survival (PFS), overall survival (OS), and safety.

Two cycles of induction chemotherapy were administered with oral vinorelbine at 60 mg/m² on days 1 and 8 and cisplatin at 80 mg/m² on day 1 every 3 weeks. If no progression was observed, patients received oral vinorelbine at 40 mg/m² on days 1 and 8 and cisplatin at 80 mg/m² on day 1 every 3 weeks for two cycles, administered concurrently with radiotherapy at 66 Gy, using conventional fractionating schedule (2 Gy/fraction).

The study enrolled 54 patients. After two cycles of induction chemotherapy, the ORR was 37%. Forty-seven out of 54 patients received concomitant chemoradiotherapy reaching a median dose of 66 Gy. Toxicities encountered were mainly G3 neutropenia (9%) and G3 radiation-induced dysphagia (4%).

One month after completion of chemoradiotherapy, the ORR was 54%, and, with a median follow-up of 37 months, the PFS and OS were 12.5 and 23.4 months, respectively. Due to the excellent tolerance profile and easier administration of the oral form, 87% of patients completed the CCRT.

In 2010, Locher et al¹¹ carried out a Phase II study of weekly cisplatin plus oral vinorelbine given concurrently with radiotherapy in patients older than 70 years, affected

by locally advanced NSCLC, with the aim to evaluate the tolerance of this CCRT scheme. The schedule included oral vinorelbine at 30 mg/m² weekly and intravenous cisplatin at 30 mg/m² weekly during 6 weeks, concurrently with chest radiotherapy until a total dose of 66 Gy. Safety was the primary end point of the study, while the secondary end points were late toxicity, QoL, global response, time to progression (TTP), and OS.

The accrual was 59 patients, but an intermediate analysis was done after the inclusion of 19 patients. Up to now, final results of the study are not yet available.

A very similar Phase II trial was published by Descourt et al;¹² the aim of the study was to evaluate the feasibility and risk–benefit ratio of CCRT using oral vinorelbine plus cisplatin and concurrent radiotherapy, administered after two cycles of cisplatin–docetaxel induction chemotherapy in locally advanced stage IIIA/B NSCLC. Patients responding to induction chemotherapy continued to receive cisplatin at 80 mg/m² every 3 weeks and oral vinorelbine at 40 mg/m² on days 1 and 8 for two cycles concomitantly with chest radiotherapy. Thirty-eight patients out of the 60 enrolled (mean age 57 years) received the concurrent chemoradiation.

No complete responses were seen. In the intent-to-treat analysis, the ORRs were 32.1% after induction chemotherapy and 41.1% after CCRT. The median PFS and OS were 9.2 and 20.8 months, respectively. Adverse effects related to CCRT were G3 and G4 neutropenia (four patients) and G3 esophagitis (one patient); no treatment-related deaths were recorded.

The authors concluded that CCRT with oral vinorelbine–cisplatin combination had a favorable risk–benefit ratio in locally advanced NSCLC.

More recently, Krzakowski et al¹³ conducted a dose-finding study on stage III NSCLC with the aim to assess the standard dose of oral vinorelbine to be administered concurrently with radiotherapy, either alone (first cohort) or in combination with cisplatin (second cohort). Oral vinorelbine was administered at an initial dose of 60 mg until a total dose of 180 mg/week, on days 1, 3, and 5, concomitantly with radiotherapy at 60 Gy.

The authors concluded that the recommended dose of oral vinorelbine was 50 mg on days 1, 3, and 5 (150 mg/week), combined with cisplatin at 80 mg/m² every 3 weeks. The response rate was promising, being 42% and 55% in the first and second cohorts, respectively.

Strøm et al¹⁴ performed a Phase III trial comparing palliative CCRT versus palliative chemotherapy alone in patients with unresectable locally advanced NSCLC with

a poor prognosis (which, normally, should not be treated with CCRT).

A total of 188 NSCLC patients with poor prognosis received four cycles of chemotherapy alone consisting of intravenous carboplatin on day 1 and oral vinorelbine on days 1 and 8, given three-weekly. The “experimental arm,” namely the CCRT arm (N=94), also received radiotherapy with fractionation 42 Gy/15, starting at the second chemotherapy cycle.

Very interesting results were seen in a subgroup of patients, namely those having a bulky disease (>7 cm). In fact, patients with tumors >7 cm did significantly benefit from CCRT, with median OS rates of 9.7 and 13.4 months in the chemotherapy arm versus CCRT arm, respectively ($P=0.001$) and 1-year survival rates of 33% and 56%, respectively ($P=0.01$). Except for a temporary decline during treatment, QoL was maintained in the CCRT arm, regardless of the tumor size.

The CCRT group had significantly more number of esophagitis cases and hospitalizations, regardless of the tumor size. The authors concluded that in patients with poor prognosis and inoperable locally advanced NSCLC, large tumor size should not be considered as a negative predictive factor, and except for those with Eastern Cooperative Oncology Group performance status 2, patients with tumors >7 cm may benefit from CCRT and oral vinorelbine may be safely used.

Singhal et al¹⁵ published the results of an open-label Phase II multicentric trial (COVeRT study), namely a prospective study enrolling 43 patients with stage III NSCLC, comprising 21 squamous cell carcinoma, 18 adenocarcinoma, and four large cell carcinoma. Patients received two cycles of oral vinorelbine 50 mg/m² on days 1 and 8 coupled with intravenous cisplatin at a dose of 50 mg/m² on days 1 and 8, to be repeated every 21 days, given concurrently with radiotherapy at 60 Gy in 30 fractions (2 Gy/fraction) using 10 MV photons and three-dimensional conformal radiotherapy.

Thirty-nine out of 43 patients completed the treatment, eleven out of 39 (28%) showed a partial response, and 28/39 (72%) had stable disease. The median PFS was 25.2 months, and the median OS was 48.3 months. Toxicities were mainly esophagitis, pneumonitis, fatigue, nausea, and dysphagia, and all of them were mild and generally manageable (being grade 1 or 2 toxicities). The authors concluded that this regimen seemed to be interesting and warranted further investigation. Table 1 describes the clinical trials using vinorelbine- and cisplatin-based CCRT.

Table 1 Oral navelbine- and cisplatin-based CCRT

Study ID	Age, years	CT	RT, Gy	No of patients	ORR, %
Beckmann et al ⁹	59 (median)	CDDP 20 mg/m ² on days 1–4 + VNR os 50 mg/m ² on days 1, 8, and 15	66	11	73
Krzakowski et al ¹⁰	57 (mean)	CDDP 80 mg/m ² on days 1 and 21 + VNR os 40 mg/m ² on days 1 and 8 (2)	66	54	54
Locher et al ¹¹	>70 (mean)	CDDP 30 mg/m ² weekly + VNR os 30 mg/m ² weekly	66	59	–
Descourt et al ¹²	57 (mean)	CDDP 80 mg/m ² on days 1 and 21 + VNR os 40 mg/m ² on days 1 and 8 (2)	66	38	41

Abbreviations: CCRT, concomitant chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; ORR, overall response rate; CDDP, cisplatin; VNR os, oral vinorelbine.

Oral navelbine in monochemotherapy given concurrently with chest radiotherapy

In 2008, Silvano et al¹⁶ published preliminary results of a Phase II study enrolling 25 elderly (>65 years) patients with locally advanced NSCLC treated with oral single-agent vinorelbine concurrently with radiotherapy, as palliative (arm A) or curative (arm B) strategy. Oral vinorelbine was given at 20 mg/m² twice weekly in concomitance with chest radiotherapy, at a mean dose of 45 Gy in the palliative arm and 60 Gy in the curative arm. Fifteen patients in arm A and ten patients in arm B were enrolled. Compliance rates to the entire treatment were 87% and 80% in arm A and B, respectively, with G3 esophagitis occurring as the most frequent acute side effect. No grade 3–4 hematological toxicity was registered. Cancer-related symptoms (such as dyspnea, chest pain, hemoptysis, and cough) were reduced in 65% of patients in arm A. In arm B, four out of ten patients experienced a complete response, with three patients having a partial response, and the remaining two patients progressed. After a 2-year follow-up, the four complete responders were still alive and disease free. Both the treatment strategies appeared to be safe and active in this poor prognosis category of patients.

Schwarzenberger et al¹⁷ in 2011 published the results of a Phase I/II study of oral vinorelbine administered once weekly at escalating doses, concurrently with weekly split dose of hypofractionated palliative chest radiation. This study included 36 locally advanced NSCLC patients treated with once weekly hypofractionated chest radiotherapy (5 Gy into two fractions 6 hours apart × 12 weeks) concurrently with oral vinorelbine. The maximum tolerated dose of vinorelbine was

80 mg/m². Dose-limiting toxicity were anemia and neutropenia; however, 53% of patients received all 12 cycles with a mean of 8.5 cycles per patient administered. The median OS was 9.9 months.

Scotti et al¹⁸ in 2012 reported an experience with neoadjuvant vinorelbine-based CCRT. Six out of 43 patients underwent monochemotherapy with oral vinorelbine. Toxicity profile reported was interesting, but, unfortunately, results concerning the monochemotherapy activity are not reliable due to the small size of patient sample.

In 2012, Chiu et al¹⁹ reported a retrospective study including 24 elderly patients (median age 70 years) with stage III NSCLC, receiving vinorelbine monochemotherapy concurrently with chest radiotherapy delivered at a median dose of 59.7 Gy, and importantly, 15 of them were treated with oral vinorelbine at 40 mg/m² weekly. Primary end point was TTP, and secondary end points were the analysis of therapy-related toxicity and ORR. All 24 patients completed the planned cycles of chemotherapy; vinorelbine was never withdrawn for intolerance. In the oral vinorelbine group, median TTP was 7 months, while in the intravenous group, it was 4.8 months; the ORR was 54.2%. The most common toxicities were radiation-induced esophagitis (62.5%), dermatitis (41.7%), pneumonitis (29.2%), and vomiting (4.2%). Vinorelbine-related toxicities were anemia (20.8%), leukopenia (37.5%), fever (8.3%), thrombocytopenia (4.2%), and infection (4.2%). These results were compared to others obtained with cisplatin/etoposide regimen, docetaxel, and gemcitabine single agent-based CCRT, and no substantial differences were observed. Table 2 reports the clinical trials using navelbine monochemotherapy-based CCRT.

Table 2 Oral navelbine monochemotherapy-based CCRT

Study ID	Age, years	CT	RT, Gy	No of patients	Results
Silvano et al ¹⁶	71 (mean)	VNR os 20 mg/m ² twice weekly	45 (A)	15	65% amelioration
			60 (B)	10	25% CR at 2 years
Schwarzenberger et al ¹⁷		VNR os 80 mg/m ² weekly	2.5 in two fractions per day (12 wk)	39	OS median 9.9 months
Scotti et al ¹⁸		VNR os monochemotherapy	–	5	–
Chiu et al ¹⁹	70 (mean)	VNR os 40 mg/m ² weekly	59.7	15	TTP 7 months

Abbreviations: CCRT, concomitant chemoradiotherapy; CT, chemotherapy; RT, radiotherapy; VNR os, oral vinorelbine; CR, complete response; OS, overall survival; TTP, time to progression; wk, week; A, arm A; B, arm B.

Conclusion

Oral vinorelbine became available for clinical use since December 2006 and has been widely used, especially as mono-chemotherapy. Despite the convenience of oral administration, mainly due to the reduction of venous thrombosis caused by the intravenous injection, the good compliance observed in elderly patients, and the low rate of hematological and gastrointestinal toxicities, only 180 patients have been treated until now. Most data have been extrapolated from small Phase I/II studies including patients older than 70 years, with acceptable Eastern Cooperative Oncology Group PS scores and sometimes eligible also for doublet cisplatin CCRT.

Vinorelbine's clinical safety profile has been well studied in elderly patients, and the drug has been shown to have the same bioavailability (38% vs 40%) in both elderly and younger patients; thus, intravenous and oral forms have shown similar pharmacokinetic and pharmacodynamic properties.

At lower doses, oral vinorelbine shows the same radio-enhancer activity when compared with the intravenous form, when used as single agent in CCRT with a palliative intent. Nevertheless, few studies have investigated its role when coupled with hypofractionated chest radiotherapy. Retrospective data reported by Chiu et al¹⁹ have shown better TTP, OS, and lower toxicity in favor of single agent vinorelbine when compared with other single antineoplastic agents used in CCRT, except for adenocarcinoma histotypes. All the other above-mentioned studies do not show differences in survival between squamous cell carcinomas and adenocarcinomas, and, because the existing literature has indicated gemcitabine²⁰ and pemetrexed²¹ as drugs of first choice for adenocarcinoma, the role of vinorelbine seems to be limited to squamous cell carcinoma. Large prospective Phase III trials are necessary to consolidate the role of oral vinorelbine-based CCRT, both alone and in cisplatin doublet-based schedule for squamous cell lung cancer.

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Author contributions

All the authors contributed to the conception and design of the article, acquisition and interpretation of data, took part in drafting the article and revising it and gave their approval of the final version.

Disclosure

The authors report no conflicts of interest in this work.

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