Review Article

Inoperable stage III non-small cell lung cancer: Current treatment and role of vinorelbine

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ABSTRACT Most lung cancer patients are diagnosed with a non-resectable disease; and around 40% in advanced stages. Stage III non-small cell lung cancer (NSCLC) is a heterogeneous disease with great variations in its clinical extent which presents a major therapeutic challenge. Although chemo-radiotherapy treatment has become the most widely used, there is currently no consensus on the best standard treatment and the experience of the therapy team plays an important role in the decision taking. We review the treatment of inoperable stage III NSCLC and the role of concomitant vinorelbine in this clinical scenario.

KEY WORDS non-small cell lung cancer; stage III; chemo-radiotherapy; chemotherapy; vinorelbine

J Thorac Dis 2011;3:197-204. DOI: 10.3978/j.issn.2072-1439.2011.01.02

Introduction

Lung cancer is the most common and deadly tumour worldwide and approximately 1.3 million patients a year die of it (1). Non-small cell lung cancer accounts for 85% of all new cases diagnosed. Most patients are diagnosed with a non-resectable disease; and around 40% in advanced stages (2). Cure is unlikely in those patients with locally advanced non-small cell lung cancer (NSCLC) who do not receive radical surgery, and patients who receive chemotherapy and concomitant radiotherapy have a 3-year survival of approximately 27% (3). However, in limited disease (stage I, II, IIIA) patients who undergo surgical resection and the administration of cytostatic treatment achieve a 5-year survival of 51% (4), with an absolute benefit of 5.4% in 5-year survival, especially in patients with a good performance status (PS) (5).

At diagnosis, at least 40% of patients are already at an advanced stage, and a third have locally advanced disease (stage III) which is defined as a tumor that exceeds the structures of the lung itself, but without clinical evidence of distant spreading. These patients form a highly heterogeneous group with controversial treatment based on the combination of surgery, chemotherapy and radiotherapy.

In the past, radiotherapy was considered the standard therapy in IIIA and IIIB but demonstrated very low survival, poor local control and early development of distant disease. Patients with inoperable stage III treated only with thoracic radiotherapy experienced a median survival of 9-11 months, 2-year survival of 10-20% and 3-year survival of 5-10% (6).

There is no current consensus on the best standard treatment and the experience of the therapy team plays an important role in the decision taking.

Treatment of inoperable stage III nonsmall cell lung cancer (NSCLC)

There are various therapeutic options for the treatment of locally advanced NSCLC. The choice of which will depend on the patient's clinical situation, closely linked to their general situation, how far advanced the tumor is on diagnosis, and the experience at the hospital.

The use of induction chemotherapy treatment began after a series of clinical trials in the mid 1980s (7,8).

In 1995, a meta-analysis based on individual data from 3,033 patients showed that combining chemotherapy and radiotherapy gave a statistically significant benefit (9). This difference was greater in those trials that had used platinum treatment, with a hazard ratio of 0.87 (P<0.005) in favor of combined chemotherapy and radiotherapy treatment.

From that time, various therapeutic designs have been

No potential conflict of interest.

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Submitted Nov 22, 2010. Accepted for publication Jan 07, 2011.
Available at www.jthoracdis.com

ISSN: 2072-1439

investigated in the search for the best treatment sequence. This review briefly explains the main studies and their findings on each of the various types of treatment.

Sequential chemotherapy and radiotherapy vs exclusive radiotherapy

The pivotal trial was performed by the Cancer and Leukemia Group B (CALGB) 8433 (10), which randomized 155 patients in a sequential model of induction chemotherapy with cisplatin-vinblastine, followed by radiotherapy with 60 Gy, versus radiotherapy at the same dose. The study showed a significant improvement for the combination arm, with a median survival of 13.8 months vs 9.7 months (P=0.0066) and a difference in 3- and 5-year survival of 23% vs 11%, and 19% vs 7%, respectively.

A three-arm confirmatory study was conducted by the Radiation Therapy Oncology Group (RTOG), Southwest Oncology Group (SWOG) and ECOG (11). It randomized 450 patients to receive exclusive radiotherapy, chemotherapy with cisplatin-vinblastine followed by 60 Gy radiotherapy, or combined treatment with hyperfractionated radiotherapy (1.2 Gy per fraction, twice a day) to a total of 69.6 Gy. Median survival was 11.4 months for patients receiving exclusive radiotherapy; 13.2 months (P=0.04) for those receiving the combination; and 12 months for hyperfractionated radiotherapy. Overall survival was statistically greater for patients who received combined treatment than for those who had radiotherapy alone.

A third study, conducted by Le Chevalier et al. (12) with 353 patients, compared three induction chemotherapy cycles (cisplatin, vindesine, cyclophosphamide and lomustine) followed by radiotherapy and three more cycles, vs exclusive radiotherapy. With an average follow-up of 40 months, two-year survival of the radiotherapy group was 14% vs 21% for the combination arm (P=0.08). A second analysis (13), with a mean follow-up of 61 months, found statistically significant benefit in overall survival at 3 years of 12% vs 4% (P =0.04) (Table 1).

After the publication of the above-mentioned the NSCLC Collaborative Group (7) meta-analysis (BMJ 1995), other meta-analyses (14,15 ,16 ,17 ,18) showed improved survival from the combination of cisplatin-based chemotherapy and radiotherapy vs radiotherapy alone, with a 5-year survival benefit of 2-4% which, although small, is considered to be clinically relevant.

Concurrent chemo-radiotherapy vs exclusive radiotherapy

Various phase-III trials compared concurrent chemo-radiotherapy treatment vs exclusive radiotherapy. One of these was conducted by the European Organization for Research and Treatment of Cancer (19) (EORTC). Time to relapse (P=0.015) and 3-year survival were significantly greater in patients receiving daily chemotherapy with cisplatin vs those with radiotherapy alone (16% vs 2%; P=0.09).

Two other trials, carried out by Jeremic et al. (20,21), analyzed the efficacy of concurrent treatment based in carboplatin plus etoposide. The group of patients with concurrent treatment showed a significant improvement in mean (22 months vs 14 months) and 4-year survival (23% vs 9%, P=0.021) (Table 2).

These trials indicate that concurrent chemo-radiotherapy clearly improves local control of the disease, which is translated into greater survival. It should also be noted that the chemotherapy doses used in these trials were lower than the doses normally used to treat systemic disease.

Sequential vs concurrent chemo-radiotherapy

Once the benefit of using chemotherapy and radiotherapy was established, the best sequence of treatment became the great unknown. The West Japan Lung Cancer Group (22) randomized 320 stage-III A and B patients to concurrent chemo-radiotherapy vs sequential chemotherapy with cisplatin, vindesine and mitomycin. Median survival was greater in patients who received concurrent treatment (16.5 vs 13.3 months; P=0.04). Overall 5-year survival was 15.8% for the concurrent, and 9% for the sequential arms. One criticism of this study is that further chemotherapy was administered to the concurrent treatment group after the protocol.

Another similar study was conducted by the RTOG (9410) (23) with 610 stage II and III patients. The chemotherapy treatment was based on cisplatin and vinblastine, and the concurrent treatment arm had significantly better overall survival than the sequential arm (P=0.046).

A phase II trial (24) randomized 102 stage III A and B patients to receive concurrent or sequential treatment with chemotherapy based on cisplatin and vinorelbine. Median survival was greater in the concurrent arm (16.6 vs 12.9 months; P=0.023); and 3-year survival was 18.6% for concurrent treatment vs 9.5%, but the treatment arms were not well-balanced to the detriment of the sequential treatment group.

The French group (25) randomized 112 patients to receiving sequential treatment with two cycles of cisplatin and vinorelbine, followed by radiotherapy, vs cisplatin and etoposide concurrent with radiotherapy. Median survival was 14.5 months for the sequential arm vs 16.3 months for the concurrent treatment arm (P=0.24) (Table 3).

The Bronchial Carcinoma Therapy Group (26) studied neoadjuvant treatment with chemotherapy followed by radiation therapy alone, or by concurrent chemo-radiotherapy in stages IIIA and B. Median survival was 14.1 months for the radiotherapy group and 18.7 months for the chemo-radiotherapy group (P=0.091). Mean time to progression was better in the concurrent treatment arm (11.5 vs 6.3 months, P=0.091), with similar toxicity.

Table 1. Studies of chemotherapy followed by radiotherapy vs radiotherapy alone

Author N° patients	Treatment	Mean survival (months)	Overall 5-year survival
Dillman[10]	•Cisplatin-Vinblastine + RT	13.8*	19%*
N: 155	•RT	9.7	7%
Sause[11]	•Cisplatin-Vinblastine + RT	13.2*	8%*
N: 458	•Cisplatin-Vinblastine +hyperfractionated RT	12	6%
	•RT	11.4	5%
Le Chevalier[12,13]	•Cisplatin-Vindesine-Cyclophosphamide-Lomustine + RT	12*	12%* (3-year data)
N: 353	•RT	10	4%

* **Statistically significant difference**

Table 2. Studies of concurrent chemo-radiotherapy vs radiotherapy alone

Author N° patients	Plan	Mean survival (months)	Overall 5-year survival
Schaake-Koning[19]	•Daily cisplatin - RT	12	10%*
N: 331	•Weekly cisplatin - RT	13	10%
	•RT	12	2%
Jeremic[20]	•Carboplatin-etoposide-hyperfractionated RT	22*	23%*
N: 169	•Carboplatin-etoposide-RT	22	16%
	•Hyperfractionated RT	14	6%
Jeremic[21]	•Carboplatin-Etoposide-Hyperfractionated RT	18*	21%*
N: 131	•Hyperfractionated RT	8	5%

* Statistically significant difference

Table 3. Phase-III studies: concurrent (C) vs. sequential (S) treatment

Author N° patients	Plan	OR (%)	Esofagitis G3-4 (%)	MST (months)	OS 5 years (%)
Furuse[22]	S	66.4	1	13.3	8.9
N: 320	C	84*	2.5	16.5*	15.8*
Curran[23]	S	59	4	14.6	12
N: 611	C	68	25	17*	21*
	C BID	64	44	15.6	17
Zatloukal[24]	S	47		12.9	15 (at 2 years)
N: 102	C	80		16.6	42
Fournel[25]	S	54	3	14.5	14
N: 212	C	49	32	16.3	21

OR: overall response; MST: median time survival; OS: overall survival; BID: twice a day; * Statistically significant difference

A review of various trials published between 2000 and 2005 concluded that 5-year survival for inoperable stages IIIA and B increased from the 7% obtained with radiotherapy alone to 10% with sequential treatment, and as much as 15% for concurrent treatment (27). A meta-analysis of 12 clinical trials with 1,921 patients at various stages analyzed the role of chemotherapy based on cisplatin associated with radiotherapy and concluded that the addition of cisplatin to radiotherapy improves survival, with absolute benefit of 4% at 2 years (P=0.02), and that the combination of cisplatin and etoposide is more effective than cisplatin alone (28).

It should be noted that toxicity increases with concurrent

treatment, particularly due to grade 3-4 esophagitis. Patients who are to undergo concurrent therapy regimes need to be selected using strict criteria to exclude those with weight loss or extensive exposure of lungs to radiotherapy.

In an attempt to unify criteria, a meta-analysis was published to clarify whether concurrent or sequential treatment is better (29). This included 1,205 patients with a 6-year follow-up, and demonstrated that concomitant treatment contributed absolute benefit on overall survival at 5 years of 4.5% (15.1% vs 10.5%) over sequential treatment. This was statistically significant (HR=0.84, *P*=0.004), but at the cost of increasing toxicity in the form of degree 3-4 esophagitis from 3 to 18% (*P*<0.0001). Grade 3-4 bone marrow toxicity increases with concurrent treatment, depending on the type of chemotherapy and the timing of control blood counts, with a range extending from 20% to 90%. Even in groups of patients with higher comorbidity, concurrent treatment is considered feasible and maintains its effectiveness (30).

Those data were confirmed in the Cochranne (31) review that included 6 studies with 1,200 patients, showing a benefit in overall survival (HR 0.74, 95% CI: 0.62~0.89) with the treatment concurrent with increased toxicity (severe esophagitis).

Role of induction chemotherapy prior to concurrent treatment

Although, as stated above, chemo-radiotherapy is a better approach than exclusive radiotherapy, the question is posed as to whether induction chemotherapy could be useful prior to concurrent treatment. The studies on induction chemotherapy are explained below.

The CALGB group compared induction chemotherapy with two carboplatin and taxol cycles, followed by concomitant chemo-radiotherapy, vs concomitant chemo-radiotherapy alone (32). Median survival in the chemo-radiotherapy arm was 11.4 months vs 14 in the induction arm (*P*=0.154), with one-year survival of 48% and 54%, respectively.

The LAMP (Locally Advanced Multimodality Protocol) phase-II randomized study compared 276 stage IIIA and B patients (33), who were randomized to receive induction chemotherapy followed by radiotherapy, induction chemotherapy followed by concurrent chemo-radiotherapy or (a third arm) concurrent chemo-radiotherapy followed by chemotherapy. The chemotherapy was with carboplatin and paclitaxel. However, the trial was closed down early due to poor recruitment without reaching sufficient statistical power for the direct comparison of the three arms. This, together with the bias of patients who experienced weight loss, the smallness of the sample and the phase-II design, makes it hard to interpret the study findings. Median survival, after a follow-up of 39.6 months, was higher in the arm receiving concurrent chemo-radiotherapy followed by chemotherapy, with a median survival of 16.3 months, vs 13 months in the sequential arm, and 12.7 months for induction chemotherapy followed by concurrent chemo-radiotherapy. All this leads to the conclusion that the most usual treatment option, as recommended by international guidelines (34,35), is definitive concomitant chemo-radiotherapy, although other options are admitted, among which are those including induction chemotherapy.

Vinorelbine: Opportunity for new therapy designs

In locally advanced stages, a plateau of chemo-radiotherapy benefits has been reached: even in the most favourable studies, median survival is no greater than 18-23 months. Therefore, it is fitting to look for combination regimes with a good risk/benefit range that patients find more comfortable and tolerate better.

At present, there are various regimes with third-generation drugs that could be eligible for treatment designs with radiotherapy as better tolerance has been shown in advanced disease. In this respect, oral cytostatics, such as vinorelbine, could play a major role. Vinorelbine, a semisynthetic alkaloid derived from vinblastine, has several interesting features that favour concomitant use with radiotherapy. One of these is that it can be taken orally. Recently, a study of advanced lung cancer showed that 75% of patients who received vinorelbine preferred the oral formula in combination with carboplatin (36). In randomized clinical trials, oral vinorelbine proved to be an effective drug in combination with cisplatin in treating locally advanced and metastatic lung cancer, and had a good safety profile (37,38,39). It is absorbed quickly with an elimination half-life of 40 hours, it binds better to plasma proteins (13%) and has a hepatic-gallbladder metabolism (40). It was shown that oral vinorelbine has about 40% bioavailability: thus, oral doses of 60 or 80 mg/m^2 vinorelbine were equivalent to endovenous doses of 25 and 30 mg/m^2, respectively (41). Food does not affect its pharmacokinetics and the drug causes less nausea and vomiting if it is administered after a light meal (42). Early vomiting after administration of oral vinorelbine does not affect its absolute bioavailability (43), however the prior administration of an antiserotoninergic drug is recommended. If vomiting does occur, the dose does not need repeating. Age does not affect the clearance of oral vinorelbine (44) and it has no interactions with cisplatin, docetaxel, paclitaxel, capecitabine, gemcitabine or cyclophosphamide (45,46). These pharmacokinetic results establish the pathways for accepting the clinical equivalence of oral vinorelbine with the endovenous formula and with equal action.

Vinorelbine has a high response rate both in advanced disease and concomitantly with radiotherapy.

Intravenous vinorelbine combined with cisplatin and radiotherapy showed its effectiveness in a phase II study in

Table 4. Comparative results of eficacy and survival of Phase II study47 of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB NSCLC.

EFFICACY	Number of patients	% Stage IIIB	Response rate after induction CT (CR+PR)	Global response after CT-RT (CR+PR)	Progression free survival (months)	Mean survival (months)	1-year Survival (%)	3-year Survival (%)
VRL + CDDP	65	60%	40%	69%	11,5	17,7	65	23
PTX + CDDP	58	48%	31%	66%	9,1	14,8	62	19
GEM + CDDP	62	37%	35%	68%	8,4	18,3	68	28

CT: chemotherapy; CT-RT: chemotherapy concomitant with radiotherapy; CR+PR: complete response and partial response; VRL + CDDP: cisplatin with vinorelbine; PTX + CDDP: cisplatin with paclitaxel; GEM + CDDP: cisplatin with gemcitabine

Table 5. Comparative results of safety and discontinuation treatment of Phase II study47 of cisplatin with gemcitabine or paclitaxel or vinorelbine as induction chemotherapy followed by concomitant chemoradiotherapy for stage IIIB NSCLC.

EFFICACY	Neutropenia	Thrombopenia	Esophagitis	Treatment discontinuation (% patients)
VRL + CDDP	27%	2%	25%	13%
PTX + CDDP	53%	6%	39%	15,5%
GEM + CDDP	51%	56%	52%	35,5%

VRL + CDDP: cisplatin with vinorelbine; PTX + CDDP: cisplatin with paclitaxel; GEM + CDDP: cisplatin with gemcitabine

Table 6. Toxicity of Phase II study48 of oral vinorelbine and cisplatin as induction chemotherapy and concomitant chemo-radiotherapy in stage III NSCLC.

Tolerance NCI/CTCV2 Grades 3-4 (n=54)	Induction CT	Conc. CT-RT
Neutropenia	28%	8,5%
Febrile neutropenia	7,4%	0%
Nausea / vomiting	15,4%/9,3%	0%/4,2%
Fatige	0%	2%
Dysphagia	0%	4% (Gr 3)
Radiation dermatitis	0%	2%

CT: chemotherapy; CT-RT: chemotherapy concomitant with radiotherapy

which comparisons were made between cisplatin/gemcitabine vs cisplatin/paclitaxel vs cisplatin/vinorelbine in 2 induction cycles followed by concomitant therapy (47). There were no differences in response or survival for any of the three treatment arms (Table 4), however there were differences in tolerance. The cisplatin/vinorelbine arm had fewer secondary effects and fewer treatment interruptions (Table 5).

The first international study of oral vinorelbine combined with cisplatin and radiotherapy was published in 2008. In this phase-II study (48), which included 54 patients, 2 cycles of cisplatin (80 mg/m^2) / oral vinorelbine (60 mg/m^2) were administered as induction therapy followed, in the case of no progression, by 2 cycles of cisplatin (80 mg/m^2) / oral vinorelbine (40 mg/m^2) concomitant with radiotherapy (66 Gy). A 54% response was obtained, evaluated by external committee, with progression-free survival of 12.5 months, overall survival of 23.4 months and 2-year survival of 48%, with a better safety profile (4% grade 3 esophagitis). It should also be noted that 76% of patients received the maximum treatment dose established by the protocol, and 87% completed the chemo-radiotherapy as planned. The study found that the main toxicity was hematological: 28% grade 3-4 neutropenia during induction and 9% during combined therapy. Of non-hematological toxicity, grade-3 dysphagia secondary to radiation was the most common, occurring in 4.3% of patients. Late pulmonary fibrosis was only seen in one patient (Table 6).

Recently, it has been published another similar study showing similar results (49). In this multicenter phase II trial, combination of oral vinorelbine (40 mg/m^2) on days 1 and 8 and cisplatin (80 mg/m^2) concomitant with radiotherapy (66 Gy) was administered after induction cisplatin-docetaxel. Of 56 patients enrolled, 38 were assessable for the tumor response. Response rates were 32.1% after induction CT and 41.1% after CT-RT. The median progression-free and overall survival

times were 9.2 months and 20.8 months. Main toxicity was neutropenia and esophagitis

Discussion

Concurrent chemo-radiotherapy improves overall survival of patients with locally advanced NSCLC, compared with sequential chemo-radiotherapy. Nowadays platinum-based polychemotherapy is considered the standard treatment. The second drugs associated to platinum seems to have no large impact in survival, so it should be choice based on its toxicity profile. Cisplatin plus vinorelbine regimen is a good candidate for combination with concurrent radiotherapy because of its efficacy and safety. These results are highly promising, being even better than other concurrent chemotherapy studies, with very good tolerance and little toxicity. This leads us to compare this model with that thought to be most active in this situation, cisplatin-etoposide, which provides a median survival of 23.2 months (overall survival at 3 years of 26.1%, progression-free survival around 10 months) (50,51,52).

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