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ORIGINAL ARTICLE

Concurrent chemoradiotherapy with vinorelbine and a platinum compound followed by consolidation chemotherapy for unresectable stage III non-small cell lung cancer: preliminary results of a phase II study

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Summary

Purpose: *To determine the efficacy, toxicity and survival of concurrent therapy with vinorelbine and a platinum compound with radiotherapy (RT), followed by consolidation chemotherapy with the same drugs, for locally advanced non small cell lung cancer (NSCLC).*

Patients and methods: *Fifty-seven patients with stage III NSCLC were included in this phase II study: median age 56 years (range 44-71), males / females 49/8, ECOG performance status (PS) 1/2 = 27/30, stage IIIA/IIIB 11/46, squamous cell carcinoma 44, adenocarcinoma 7, adenoid cystic carcinoma 1 and large cell carcinoma 5. Treatment consisted of 2 cycles of chemotherapy with vinorelbine and cisplatin or carboplatin, given concurrently with RT, followed by 2-4 more cycles of consolidation chemotherapy with the same drugs. Twenty-two patients received amifostine for radio- and chemoprotection.*

Results: *Grade 3 or 4 toxicities were neutropenia and esophagitis in 19% of the patients each, and gastrointestinal toxicity in 17% of the patients. Of the 55 patients evaluable for response, 23.64% achieved complete response (CR) and 40% partial response (PR) (overall response rate 63.64%). Progression -free survival curves showed 1- and 2-year values of 42% and 21%, respectively, and median time to progression 10.5 months. The 1- and 2-year disease-specific survival was 58% and 29%, and the median overall survival 15 months.*

Conclusion: *Preliminary analysis indicates that concurrent vinorelbine and a platinum compound with RT followed by consolidation chemotherapy with the same drugs for advanced stage III NSCLC is well tolerated, has considerable activity and positive impact on survival.*

Key words: advanced, concurrent chemoradiotherapy, non small cell lung cancer, platinum compound, vinorelbine

Introduction

Lung cancer still remains a serious health problem worldwide. It is the leading cause of cancer mortality, especially in men, in many countries and its incidence has an alarming increasing rate of 0.5%. NSCLC comprises the vast majority (75%) of all lung cancers, with approximately 60-70% of patients presenting with locally advanced inoperable disease. This group includes bulky stage IIIA and IIIB disease, excluding malignant pleural effusion [1]. In the last decades, big efforts have been made with an aim to improve local control and survival, influencing the evolution of treatment strategies. Before the 1980s, external beam thoracic RT has been the standard therapy for advanced NSCLC, but only few patients achieved CR, the median survival ranged from 6 to 11 months, and the 5-year survival was only 3-7% [2]. From the 1990s on, the benefits of combined chemoradiotherapy strategies have been explored, first sequentially [3-5], then in concurrent regimens [6-8], achieving improved sur-

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vival over RT alone, with a median survival of 13-14 months and 5-year survival as high as 15-20% (3-fold increase over RT alone) [9]. Low dose daily cisplatin with conventionally fractionated RT showed significant locoregional free survival (LRFS) and overall survival benefit compared with RT alone in an EORTC study [8]. Currently, a large body of evidence supports concurrent chemoradiotherapy as the prefered therapeutic option for patients with good PS and unresectable locally advanced NSCLC in order to improve both local and distant control. The results of 4 randomized studies indicate that concurrent chemoradiation is superior to the sequential approach in terms of overall survival [10-13], but at a price of higher toxicity.

The efficacy of consolidation chemotherapy after chemoradiotherapy with an aim to further improve systemic control has been examined in several studies [9,14].

Combinations of platinum compounds with 3rd generation drugs (antimicrotubule agents, topoisomerase inhibitors) have been evaluated, showing promising activity [5,9].

It seems that the benefit of concurrent chemoradiation is been achieved at the expense of higher toxicity, thus making the role of protecting factors important.

The aim of this study was to determine the efficacy, toxicity and survival of concurrent chemotherapy with vinorelbine and a platinum compound with RT, followed by consolidation chemotherapy with the same drugs in locally advanced stage III NSCLC.

Patients and methods

Eligibility criteria

Previously untreated patients, with histologically documented, inoperable stage IIIA or IIIB NSCLC, with good PS (ECOG 1 – 2), weight loss less than 10% during the last 3 months, were eligible for the study. All patients had measurable disease, adequate hematologic, renal and hepatic functions (neutrophil count $\geq$ 1800/ml, platelet count $\geq$ 100.000/ml, haemoglobin $\geq$ 10 g/dl, creatinine level < 1.5 mg/dl, bilirubin < 1.5 times the upper limit of normal (ULN), AST < 2 times the ULN. Before initiation of the protocol therapy all patients had physical examination, complete blood cell count, serum biochemistry, postero-anterior and lateral chest radiograph and computed tomographic (CT) scan of the chest and upper abdomen to include the liver and adrenal glands. Brain CT scan and bone scan were performed only when symptoms or biochemistry findings were suggestive of central nervous system or skeletal metastases.

Exclusion criteria

Excluded were patients over 75 years with PS 3-4, with pleural effusion, serious medical or psychiatric illnesses, other malignancies (except carcinoma of the skin) or not suitable to a regular follow-up due to social or geographical reasons.

Treatment plan

Patients received 2 cycles of chemotherapy with vinorelbine and a platinum compound concurrently with RT, followed by 2-4 more cycles of consolidation chemotherapy with the same drugs. When given concurrently with RT the drugs were administered at lower doses: vinorelbine (15 mg/m^2 given as an i.v. infusion over 30 min on days 1 and 8, every 21 days) and cisplatin (80 mg/m^2 i.v. infusion over 2 h with hydration on day 1), or carboplatin AUC 2.5, every 21 days. When given as consolidation chemotherapy the doses were: vinorelbine 25 mg/m^2 days 1 and 8, every 21 days; cisplatin 100 mg/m^2, day 1, or carboplatin AUC 5, day 1, every 21 days. Fifty-four patients received cisplatin and 3 carboplatin. Premedication with dexamethasone and antiemetics was administered routinely. Twenty-two patients received the organic thiophosphate radio / chemoprotector amifostine (ethyol WR-272) before chemotherapy as a 30 min i.v. infusion at a dose of 740 mg/m^2, on days 1 and 8, every 21 days.

RT started concomitantly with chemotherapy, usually on the first day of treatment. Delays due to technical reasons (3 cases) did not exceed the first week. RT was delivered with 15 MV linear accelerator. CT scan was used for target volume delination. Two different target volumes were considered: the initial large-field target volume consisting of the primary tumor and the mediastinal lymph nodes and the boost target volume consisting of the primary tumor and the proximal involved lymph nodes. The total dose of the involved area was 56-60 Gy/28-30 fractions in 5.5 - 6 weeks.

Statistical analysis and response criteria

The study was designed for a statistical power of 80% for detecting a benefit of 20% in response rate (CR and PR), from 40% to 60%. In this case the total accrual should be at least 73 patients for a unilateral test, and 94 for a bilateral test. The false positive error rate

was chosen at $\alpha = 0.05$. Statistical significance was set at the 0.05 level and 95% confidence interval (CI) was estimated by the binomial distribution function [15].

The primary statistical analysis consisted of an estimation of the CR and PR rate. Response Evaluation Criteria in Solid Tumours (RECIST) were used to assess response [16]. CR was defined as the disappearance of all measurable lesions. PR required a decrease of at least 50% in the sum of the longest diameters of the measurable lesions, taking as reference the baseline sum of longest diameters. Once a CR or PR was achieved, tumor assessment was done no less than 4 weeks after the criteria for response were first met, to confirm the response. Progressive disease (PD) was defined as an increase of at least 20% in the sum of the longest diameters of the measurable lesions, taking as reference the smallest sum recorded since the start of treatment or the appearance of new lesions. Stable disease (SD) was defined as neither sufficient shrinkage to qualify for PR, nor sufficient increase to qualify for PD, taking as reference the smallest sum recorded since the start of treatment. The response rate (RR) was calculated as the ratio of the number of complete and partial responders to the total number of evaluable patients.

Response was evaluated in all of the cases by CT scan of the chest and abdomen, 4-6 weeks after the last chemotherapy cycle. Evaluations during treatment were carried out by chest radiographs and patients with objective response and good tolerance received 2 more cycles of consolidation chemotherapy, to a total number of 6 cycles.

Secondary analysis included disease-specific and progression-free survival, considered from the date of starting treatment until PD. Survival curves were constructed according to the Kaplan-Meier method.

Endpoints

The following endpoints were considered: evaluation of toxicity (according to WHO and RTOG criteria); response rate (according to RECIST criteria); survival (estimated by the product limit method of Kaplan- Meier curve); and time to progression.

Results

Patient characteristics

Between 16.11.2000 and 18.09.2003, 57 patients were enrolled. Patient characteristics are listed in Table 1. The median age was 56 years (range 44-71), with male prevalence (86% of the cases). PS was distributed almost equally between 1 (47%) and 2 (53%) patients. Eleven (19%) patients had stage IIIA, 46 (81%) IIIB. The most common histologic type was squamous cell carcinoma (77%). Adenocarcinoma was present in 13%, large cell carcinoma in 8% and adenoid cystic carcinoma in 2% of the cases.

Table 1. Patient characteristics (n=57)

Characteristic	*Patients, n*	*%*
Median age (years)	56	
Range	44-71	
Sex		
Male	49	86
Female	8	14
Perfomance status (ECOG)		
1	27	47
2	30	53
Histology		
Squamous cell	44	77
Adeno	7	13
Large cell	5	8
Adenoid cystic	1	2
Stage		
IIIA	11	19
IIIB	46	81

Treatment compliance and toxicity

All 57 patients were evaluable for toxicity. 225 chemotherapy cycles were administered, with a mean value of 3.9 cycles per patient. At least 4 cycles of chemotherapy (2 concurrent and 2 consolidation) were completed by 37 (65%) patients, whereas 45 (79%) patients completed the optimal dose of RT.

One patient developed grade 3 renal toxicity and grade 4 neutropenia after the first cycle of chemotherapy, resulting to septic death. One patient with grade 4 gastrointestinal toxicity after the first cycle abandoned treatment. Eighteen patients didn't complete cycle 3 or 4 of chemotherapy because of esophagitis, gastrointestinal toxicity or PD. Eleven patients didn't complete the optimal dose of RT because of toxicity, mainly esophagitis, or PD. One stage IIIA patient achieved downstaging after 40 Gy and 3 cycles of chemotherapy and expressed his option for surgery.

Toxicity is described in Table 2. There was a preponderance of mild, grade 1 and 2 toxicity. Severe grade 3 and 4 toxicity was neutropenia in 11 (19%), esophagitis in 11 (19%) and nausea and vomiting in 10 (17%) patients.

There was a trend for less severe esophagitis among patients who received amifostine, but without reaching statistical significance (Table 3).

Table 2. Toxicities encountered

Toxicity	*Grade* 1 *Patients, n*	2 *Patients, n*	3 *Patients, n*	4 *Patients, n*	3+4 *Patients, n (%)*
Neutropenia	7	6	9	2	11 (19)
Thrombocytopenia	8	1	–	–	–
Anemia	9	5	4	–	4 (7)
Nausea/vomiting	14	12	9	1	10 (17)
Esophagitis	16	11	10	1	11 (19)
Renal	1	–	1	–	1 (1)
Skin	2	2	–	–	–
Neuropathy	1	2	–	–	–
Dyspnea	2	3	–	–	–
Lung fibrosis	1	6	–	–	–

Response and survival

Fifty-five of 57 patients were evaluable for response (Table 4). Thirteen patients achieved CR (23.64%; 95% CI 12-35) evaluated by thoracic CT. In 4 patients CR was also evaluated by bronchoscopy. Twenty-two patients achieved PR (40% ; 95% CI 27-53) for an overall RR of 63.64% (95% CI 50.9-76.4). Sixteen patients showed SD (29.09% ; 95% CI 17-41), and 4 had PD (7.27% ; 95% CI 0-14). RR (Table 5) was significantly higher (p= 0.01) in patients who received at least 4 cycles of chemotherapy (75.68%) vs. those who received less than 4 cycles (38.9%). The RR for patients who completed at least 56 Gy was 66.7% vs.

Table 3. Toxicities according to administration of amifostine

Toxicity	*Patients with amifostine (n = 22)* *Gr 3 Patients, n*	*Gr 4 Patients, n*	*Gr 3+4 Patients, n (%)*	*Patients without amifostine (n= 35)* *Gr 3 Patients, n*	*Gr 4 Patients, n*	*Gr 3+4 Patients, n (%)*	*p-value*
Neutropenia	3	1	4 (18)	6	1	7 (20)	
Gastrointestinal	3	1	4 (18)	6	0	6 (17)	
Esophagitis	2	1	3 (14)	8	0	8 (22)	0.75

Table 4. Responses according to number of post chemoradiotherapy courses

Treatment	*CR n (%)*	*PR n (%)*	*SD n (%)*	*PD n (%)*	*Total no. of pts*
RT & 2 cy	2 (66.7)	– (–)	– (–)	1 (33.3)	3
RT & 2 cy + 1 cy post RT	1 (6.7)	4 (26.7)	8 (53.3)	2 (13.3)	15
RT & 2 cy + 2 cy post RT	5 (22.7)	11 (50.0)	5 (22.7)	1 (4.6)	22
RT & 2 cy + 3 cy post RT	1 (16.7)	2 (33.3)	3 (50)	– (–)	6
RT & 2 cy + 4 cy post RT	4 (44.4)	5 (55.6)	– (–)	– (–)	9
Total no. of pts (%)	13 (23.64)	22 (40)	16 (29.09)	4 (7.27)	55
95% CI	12-35	27-53	17-41	0-14	

cy: cycle of chemotherapy, CR: complete response, PR: partial response, SD: stable disease, PD: progressive disease, CI: confidence interval, RT: radiotherapy

Table 5. Responses according to the number of chemotherapy cycles

No of cycles	*CR & PR n (%)*	*SD & PD n (%)*	*Total no. of pts n*	*p-value*
< 4	7 (38.89)	11 (61.11)	18	
≥ 4	28 (75.68)	9 (24.32)	37	< 0.01
Total no. of pts (%)	35 (63.64)	20 (36.6)	55 (100)	

For abbreviations see footnote of Table 4

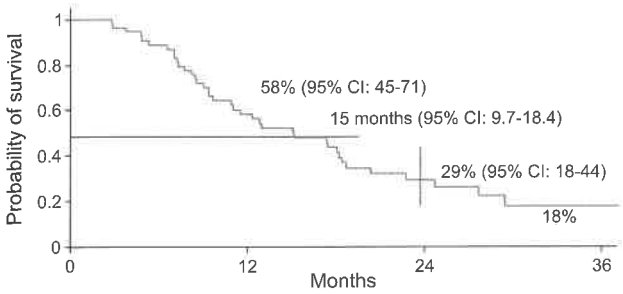


Figure 1. Disease-specific survival.

50% for those who didn't receive the optimal dose of RT, but the difference didn't reach statistical significance (p=0.53). For the patient who underwent surgery the microscopic findings revealed only isolated islands of squamous cell carcinoma in a mass of fibrosis and negative lymph nodes.

The 1- and 2- year disease-specific survival rates were 58% and 29%, respectively (Figure 1) and the median survival was 15 months (95% CI 9.7-18.4). The progression-free survival (Figure 2) showed 1- and 2- year values of 42% and 21%, respectively, with a median time to progression of 10.6 months (95% CI 8.1- 15.3). For the 17 patients who are still alive the median follow up time was 19 months.

Patterns of failure

Of the 41 patients who progressed, 20 (35%) developed locoregional failure, 12 (21%) distant metastases alone and 9 (15%) developed both distant and locoregional failure. Of the patients with distant metastases, bones and brain were the most common sites of failure, in 8 and 7 cases, respectively (Table 6). Three patients developed metastases in the liver, 2 in the adrenals and one in the pancreas.

Discussion

Stage III NSCLC is very heterogeneous, with locally extensive tumors and invasion of the mediastinal lymph nodes, with low overall survival due to modest local control and development of distant failures. Thus the treatment of stage III patients should aim at both local and systemic disease control. Therefore, combined modality treatment has become standard approach. Still, the optimal therapy for locally advanced, stage III NSCLC is debated and many questions are waiting for answers concerning the best drug combinations, the sequencing issue with RT, the use of protectors, integration of new RT techniques, and, finally, new biological agents. Randomized clinical trials and metaanalyses support the conclusion that cisplatin-based chemotherapy in combination with RT improves survival compared with RT alone [17,18]. With the advent of 3rd generation drugs (antimicrotubule agents, topoisomerase inhibitors), new combinations with or without platinum compounds have been evaluated [19-22]. Preclinical studies, indicating a role for vinorelbine as radiosensitiser, based on the antimicrotubule effect with subsequent cell cycle arrest in G2/M (the most radiosensitive cell cycle phases), have led to the use of vinorelbine /cisplatin combination plus RT. A series of published studies have shown that the sequential administration improves survival from 9.6 to 13.7 months [3]. However, local control remains an issue of concern, as 31-50% of patients experience locoregional failure inside the radiation field, which has led to concomitant approaches achieving a response rate from 44% to 76% and a median survival from 10 to 16.6 months (Table 7) [23-27]. The outcomes of our study are comparable with these data. Furthermore, a recent randomized trial [13] has shown significantly better results in terms of survival for the concomitant vinorelbine / cisplatin/ RT approach than the sequential one (median survival 16.6 months vs. 12.9, 3-year survival 19 vs. 9, respectively). Nevertheless, these results were obtained at the cost of higher toxicity such as esophagitis (17%) and neutropenia (64%), which led to the use of chemo-radio-protectors and colony stimulating factors. Still it is debated if concurrent chemoradiotherapy preceeded by induction chemotherapy is better than followed by consolidation

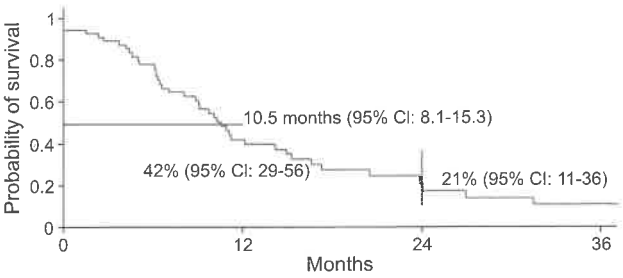


Figure 2. Progression-free survival.

Table 6. Sites of distant failures

Site	*No. of patients*	*%*
Bone	8	16
Brain	7	12
Liver	3	5
Adrenals	2	3
Pancreas	1	2

Table 7. Vinorelbine combinations with concomitant radiotherapy in locally advanced NSCLC

Study	*Treatment (mg/m²)*	*No. of patients*	*Stage (%)*	*RR (CR %)*	*Median overall survival (mo)*
Masters USA [23]	Nvb: 15-25 d1+8/cis: 80-100 d1 q 3w +RT 60 Gy	32	III: 59 IV: 41	47 31	10
Bover Spain [24]	Nvb: 15-25 d1+8 /cis: 100 d1 q 3w +RT ≥ 60 Gy	36	IIIA: 36 IIIB: 64		16.6
Kisohara Japan [25]	Nvb: 20 d1+8 /cis: 80 d1 q 3w +CHART 61 Gy	26		70 (8)	NR
Cohen USA [26]	Nvb: 15 d1+8/ CBDCA: AUC 1.5-3 q 3w x 2cy + RT 60-70 Gy	33	III: 78 IV: 22	51 (6)	NR
Hoffman USA [27]	Nvb: 15 d1/ CBDCA: AUC 1.5-3 d1 w1,2,4,5 + RT 60-70 Gy	22	IIB: 3 IIIA: 26 IIIB: 41 IV: 30	54 (45)	NR

Nvb: vinorelbine, Cis: cisplatin, CHART: continuous hyperfractionated accelerated radiotherapy, CBDCA: carboplatin, AUC: area under the curve, d: day, w: week, NR: not reported, mo: months, cy: cycle

chemotherapy. The SWOG 9504 trial reported encouraging results regarding the consolidation chemotherapy after the concurrent sequence, with a 3-year survival rate of 40% [14]. The CALGB study [28] randomized three 3rd generation drug combinations: cisplatin combined with gemcitabine, paclitaxel and vinorelbine, respectively. Two cycles were given as induction chemotherapy followed by 2 more cycles given concurrently with RT. The recent data showed comparable results in relation with RR and survival for the 3 arms. For the vinorelbine / cisplatin / RT arm the RR was 67% with a median survival of 18.4 months and 1-, 2-, and 3-year survival rates of 65%, 40%, and 23%, respectively, along with the most favorable toxicity profile (grade 3 and 4 neutropenia 27%, thrombocytopenia 2%, esophagitis 24%) compared with the other arms. The RR and toxicity profile in our study was comparable with these data. The patient who developed grade 4 neutropenia with septic death after the first cycle of chemotherapy was considered as a possible consequence of a latent nephropathy, which led to renal failure.

Conclusions

Preliminary analysis of our study indicates that concurrent vinorelbine and a platinum compound with RT followed by consolidation chemotherapy with the same drugs for advanced stage III NSCLC is feasible and well tolerated, and the toxicity profile compares favorably with other similar studies. The major acute side effects (esophagitis and neutropenia) were at an acceptable rate and manageable. There was a trend of less esophagitis when amifostine was administered. The effect on the response rate and survival was promising and warrants further clinical evaluation in a phase III study. Also, of interest would be the integration of innovative RT techniques like 3D-CRT, with dose escalation and the addition of targeted therapies in a multidisciplinary therapeutic setting.

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