Journal of BUON **9:** 167-172, 2004

ORIGINAL ARTICLE

Split course radiation with concurrent vinorelbine and cisplatin in locally advanced non-small cell lung cancer. A phase II study

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Summary

Purpose: *Recent results coming from large randomized trials suggest that for locally advanced non-small cell lung cancer (NSCLC), integration of chemotherapy (CT) with irradiation (RT) should be concurrent rather than sequential. This study aimed at evaluating the actually delivered RT and CT dose intensities (DI), along with the toxicity and efficacy of a split course RT program with concurrent CT.*

Patients and methods: *From October 2000 to September 2002, 24 patients with histologically or cytologically documented NSCLC were included. Patients' characteristics were as follows: males/females=22/2, median age=59 years, stage IIIB/IIIA=22/2 patients, ECOG PS 0-1=15 (62%) and PS 2=9 (38%). Histology: adenocarcinoma/squamous cell/large cell/unclassified 10/6/1/7, respectively. Four cycles of vinorelbine (VNB) 25 mg/m² and cisplatin (CDDP) 40 mg/m² on days 1+8 were administered (days 1,8,22,29,57,64,78,85). Concurrent with the second CT cycle, RT (2 courses of 30 Gy separated by a 2-week break) was delivered, with a plan to achieve a total dose of 60 Gy, with a fractionation schedule of 2 Gy/day/5 days weekly.*

Results: *The intended RT dose was delivered to 21 (88%) patients with a relative DI of 0.93. Nineteen (79%) patients received more than 3 CT cycles. The relative DI for VNB and CDDP were 0.88 and 0.83, respectively. During treatment 3 (13%) patients experienced WHO grade 3-4 hematologic toxicity while ECOG grade 3 esophagitis was recorded also in 3 patients. At the end of treatment 14 (58%) patients achieved an objective response (2 complete - CR and 12 partial response - PR), while 8 (33%) patients had stable disease (SD) and 2 (8%) progressive disease (PD). After a median follow up of 15 months (range 3-26), 15 (62%) patients relapsed. There were 8 (33%) patients with local relapse and 7 (29%) with distant metastases. The median progression free (PFS) and overall survival (OS) were 10 (range 2-24) and 15 (range 5-24) months, respectively, with an estimated 1 and 2-year survival rates of 55% and 10%, respectively.*

Conclusion: *Our concurrent schedule allows for good CT and RT DI, with low associated toxicities. The efficacy data are considered promising, taking into account the high proportion of stage IIIB patients evaluated.*

Key words: cisplatin, concurrent chemo-radiation, dose intensity, non-small cell lung cancer, toxicity, vinorelbine

Introduction

Locally advanced, unresectable non-small cell lung cancer represents about 35-40% of the newly diagnosed cases of NSCLC [1]. Despite the fact that some controversies are pending on the optimal treatment of this condition [2], the combined modality treatment, including CT and RT, became the most widely accepted therapeutic approach during the last decade [3,4]. While the sequential approach was more popular during the early 1990's, concurrent CT+RT became more appealing nowadays, after the publication of better results with the concurrent strategy in 2 large randomized trials [5,6].

The rationale for concurrent CT+RT can be summarized as follows: a) spatial cooperation of the

Received 26-03-2004; Accepted 04-04-2004

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two modalities; b) CT sensitisation of RT action by: decreased recovery from potentially lethal damage, perturbation in cell kinetics with an increase in the proportion of cells in a sensitive phase of the cell cycle, decreased tumor bulk and improved blood supply leading to reoxygenation and increased sensitivity to RT [1]. In this regard, the combination of CDDP and VNB seems appropriate to be tested concurrently with RT. Both CDDP [7] and VNB [8] showed radiosenzitizing properties *in vivo*, while the combination of the two is considered one of the choices for first-line CT of advanced NSCLC [9].

The most troublesome problem with the concurrent CT+RT approach was the high rate of treatment-related toxicity [1,10], which could dictate the reduction of total dose and DI of both CT and RT, consequently affecting the antineoplastic efficacy of this strategy.

This study was aimed to evaluate the actually delivered RT and CT DI, along with the toxicity of a split course RT program with concurrent CT (VNB +CDDP), for patients with locally advanced NSCLC (inoperable stage IIIA and IIIB). Secondary objective was the evaluation of treatment efficacy (response rate, PFS and OS) for the patients treated according to this protocol.

Patients and methods

Eligibility criteria

To be eligible for inclusion, patients had to have cytologically or histologically proven NSCLC, inoperable stage IIIA or stage IIIB (without pleural effusion), no prior CT or RT, no prior history of malignancy except nonmelanoma skin cancer and *in situ* carcinoma of the cervix, age <65 years, ECOG performance status 0-2, weight loss <5% in the last 6 months, good renal (serum creatinine <1.2 mg/dL), hepatic (serum bilirubin <1.5 mg/dL) and hematologic (white blood cell - WBC count > 4,000/μL and platelet count >100,000/μL) functions, no previous neurologic disease, no recent (< 3 months before treatment) myocardial infarction and no active congestive heart failure or cardiac arrhythmia.

Pretherapeutic and follow-up patient evaluation

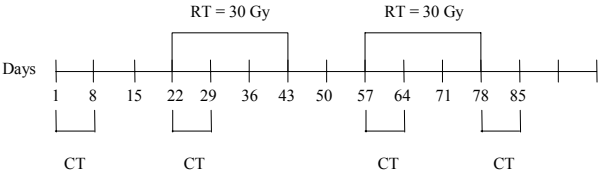
The initial workup consisted of a complete history and physical examination; fiberoptic bronchoscopy with biopsy and cytologic brushing; chest X-ray; computed tomographic evaluation of the thorax, brain and abdomen; serum biochemistry, including serum creatinine and liver function tests; complete blood cell count; and ECG. Clinical examination serum biochemistry and WBC and platelet count were performed before each CT cycle. Patients were staged using clinical criteria, according to the International System for Staging Lung Cancer, revised in 1997 [11]. Imaging evaluation was performed after the end of treatment. Patients were followed up every 3 months with clinical, chest X-ray and biological tests.

Treatment strategy

Four cycles of VNB 25 mg/m² +CDDP 40 mg/m² on days 1+8 were administered (days 1, 8, 22, 29, 57, 64, 78, 85). Concurrent with the second CT cycle, RT (2 courses of 30 Gy separated by a 2-week break) was delivered with a plan to achieve a total dose of 60 Gy with 2 Gy/day/5 days weekly for the gross tumour volume (Figure 1).

Chemotherapy administration

VNB was administered as a short intravenous (i.v.) infusion over 10 min. Rapid i.v. administration of 250 ml NaCl 0.9% was recommended after VNB infusion, to avoid venous wall injury. CDDP was administered i.v. in 250 ml NaCl 0.9% during 30 min, followed by 250 ml manitol i.v. administration in 30 min. Before and after CDDP, 2-hour hydration with 1 L of either NaCl 0.9% or dextrose 5% was carried out. Patients were instructed to continue a high liquid intake at home for 2 days. Half an hour before CDDP, 150 mg hydrocortisone hemisuccinate and 8 mg ondansetron were administered with a short i.v. infusion. Ondansetron was repeated at 4 and 8 h after the first dose. CDDP was administered at 50% of the planned dose if serum creatinine increased to greater than 1.5 mg/dL, and was stopped if its level was above 3 mg/dL. In case of myelotoxicity treatment was postponed for 1 week, or until the WBC count increased to >4,000/μL and platelet count > 100,000/μL. Packed red cells transfusion was recommended for Hb level < 8 g/dL.



CT: chemotherapy, RT: radiotherapy

Figure 1. Treatment schedule.

Radiation therapy

The original volume included the primary disease site with a margin of 2 cm around the mass and the ipsilateral hilum. The entire width of the mediastinum was included, with a margin of 2 cm around the radiographically visible area of involvement (pre-treatment chest film and CT scan). The inferior margin was extended to 4 cm below the carina or 2 cm below the radiographically demonstrated tumour mass. The ipsilateral supraclavicular fossa was treated whether or not there was any clinically involved lymph node. The RT dose for the gross tumor volume was planned to reach 60 Gy (2 Gy/day, 5 days/week), while for clinically uninvolved sites the RT dose was planned to reach up to 50 Gy. For RT delivery a 6-10 MeV linear accelerator device was used.

Evaluation of response and toxicity

Response and toxicity in this study were evaluated in accordance with the WHO criteria [12], but grading of esophageal radiation toxicity was evaluated according to ECOG criteria [13]. CR was defined as the disappearance of all measurable lesions for at least 4 weeks. PR was defined as >50% decrease in the sum of the products of the greatest perpendicular diameters of all measurable lesions for at least 4 weeks without the development of new lesions. SD was defined as <50% reduction or < 25% increase in the products of the greatest perpendicular diameter of all lesions without any evidence of new lesions for at least 4 weeks. PD was defined as an increase of >25% of the existing lesions, or the appearance of new lesions.

Evaluation of CT and RT dose intensity

The CT DI was evaluated separately for VNB and CDDP. The intended DI was calculated using the protocol doses, considering the doses and CT intervals without any modification. The actually delivered DI was calculated considering the patients' records, taking into account the dose modifications and CT delays. The DI for CT was expressed as mg/m²/week. The same method was used to express the RT DI, which was measured as Gy/day. The relative DI (actually delivered DI/intended DI ratio) was calculated for both CT and RT.

Statistical analysis

Median PFS and OS were determined using the Kaplan-Meier method. Statistical analysis was performed using the SPSS 10.0 program for Windows [14].

Results

Patient characteristics

From October 2000 to September 2002, 24 patients with histologically or cytologically documented NSCLC were included. Patient characteristics are presented in Table 1.

Chemotherapy and irradiation dose and dose intensity

The intended RT dose of 60 Gy was delivered to 21 (88%) patients. The actually delivered RT DI for all the patients was 1 Gy/day, with a relative DI of 0.93. For VNB the actually delivered DI was 12.5 mg/m²/week with a relative DI of 0.88, while for CDDP the actually delivered DI was 19.8 mg/m²/week with a relative DI of 0.83. Nineteen (79%) patients received more than 3 CT cycles (Table 2). The protocol presumed 2 CT cycles concurrent with RT, which were delivered to 13 (54%) patients, while 9 (38%) patients received 1.5 cycles, and 2 (6%) patients only 1.

Toxicity

During the protocol, 3 (13%) patients experienced grade 3-4 hematologic toxicity, while grade 3 esophagitis was recorded also for 3 patients. The detailed toxic events are presented in Table 3.

Table 1. Patient characteristics (n=24)

Characteristic	*No. of patients*	*%*
Age (years)		
median	59	
range	28-74	
Sex		
male	22	92
female	2	8
Stage		
III A	2	8
III B	22	92
ECOG performance status		
0-1	15	62
2	9	38
Histology		
adenocarcinoma	10	41
squamous cell	6	25
large cell	1	5
positive cytology	7	29

Table 2. Chemotherapy and irradiation dose and dose intensity

	Total dose delivered	*Intended DI*	*Actually delivered DI*	*Relative DI*
RT	60 Gy – 21 patients (88%)			
	50-60 Gy – 2 patients (8%)	1.07 Gy/day	1 Gy/day	0.93
	< 50 Gy – 1 patient (4%)			
VNB	–	14.2 mg/m^2/wk	12.5 mg/m^2/wk	0.88
CDDP	–	22.8 mg/m^2/wk	19.8 mg/m^2/wk	0.83
CT	4 cycles – 12 patients (50 %)			
	3.5 cycles – 7 patients (29%)			
	3 cycles – 3 patients (13%)			
	2 cycles – 2 patients (8%)			

For abbreviations see text

Table 3. Chemotherapy and irradiation associated toxicities

Toxicity	*Grade 1*	*Grade 2*	*Grade 3*	*Grade 4*
Hematological				
anemia	2	4		
leucopenia	3	1	1	1
thrombocytopenia			1	
Renal	3			
Neurologic	1	1		
Esophagitis	4	8	3	
Pneumonitis		2		

Figure 2. Kaplan-Meier curve of progression-free and overall survival.

Resonse rates and survival data

At the end of the protocol 14 (58%) patients achieved an objective response (2 CR and 12 PR), while 8 (33%) patients had SD and 2 (8%) PD. After a median follow up of 15 months (range 3-26) 15 (62%) patients relapsed. There were 8 (33%) patients with local relapse and 7 (29%) with distant metastases. The median PFS and OS were 10 (range 2-24) and 15 (range 5-24) months, respectively, with an estimated 1 and 2-year survival rate of 55% and 10%, respectively (Figure 2).

Discussion

Locally advanced, unresectable non-small cell lung cancer, represents about 35-40% of the newly diagnosed cases of NSCLC [1]. Combined modality treatment, including CT and RT was considered standard treatment of this condition, during the last decade[3]. The landmark randomized study that imposed the combined modality treatment was the CALGB 8433 [15], which showed that 2 neoadjuvant CT cycles followed by definitive RT demonstrated a clear survival benefit over RT alone. The confirmatory RTOG study [16], as well as other similar trials [17] along with the results of a Cochrane review [18] established the sequential CT- RT approach as gold standard for this condition.

The next step in order to improve the patients' outcome was to explore the impact of concurrent administration of both CT and RT. Two large randomized trials [5,6]) proved the superiority of concurrent administration over sequential CT-RT in terms of overall survival. However, both those trials, along with other phase II studies showed an increase in treatment-related toxicities (mainly haematological and esophagitis) with concurrent administration [1,10]. For

instance, a retrospective analysis of 585 patients included in 4 RTOG trials, who received concurrent CT+RT showed that 76% of the patients developed esophagitis ≥grade 2, and 37% ≥grade 3 during the protocol [19]. Irradiation-induced pneumonitis was recorded in 62% of the patients. In this context, it is mandatory to remember that for optimal efficacy, both CT and RT should be delivered at full doses and optimal intervals, and CT should not be administered to compensate an inadequate RT total dose [1]. Moreover, the time factor seems to be crucial in achieving the desired antitumoral effect. In this regard, it is important to consider the total duration of the whole protocol, from the first therapeutic intervention until the completion of treatment. The shortest this interval, the better the result will be achieved [20,21].

Our experience with concurrent CT+RT reflects the above mentioned pitfalls. Two previous studies recorded an incidence of grade 3-4 esophagitis in 32-34% of the patients. The intended RT dose of 60 Gy had to be reduced for 44 and 69% of the patients respectively, the toxicity of the combined treatment being the main reason for dose reduction [22,23]. In order to overcome the toxicity of the protocol, we designed a split course RT program, with a 14-day break after 30 Gy. The study of Furuse et al. [5] offered us the background of this solution. They applied this strategy, and obtained a good therapeutic index: median survival 16.5 months, and negligible grade 3-4 esophageal toxicity. Following the same goal we chose a low-toxicity, day 1+8 schedule, with VNB and CDDP.

The results of our study show that 88% of the patients received the intended 60 Gy of RT, with a relative DI of 0.93. The actual delivered DI for VNB was 12.5 mg/m²/week (relative DI=0.88) while for CDDP the same parameter was 19.8 mg/m²/week (relative DI=0.83). The DI of both CT and RT could be considered within a good range. It is also worth noticing that almost 80% (19 patients) received at least 3.5 cycles of CT. The treatment-related toxicity was quite low, with only 3 (13%) patients experiencing grade 3-4 hematologic toxicity, while grade 3 esophagitis was recorded also in 3 patients. In terms of efficacy, our data shows an overall response (OR) rate of 58%, and a median PFS and OS of 10 months and 15 months, respectively. The previous 2 studies conducted at our institution using concurrent CT+RT, showed an OR rate of 48 and 45%, median OS 14 months (both studies), and 2-year survival 14 and 10%, respectively [22,23]. However, the results of the present study could be considered superior, taking into consideration that the previous studies included only stage IIIA patients with ECOG performance status 0-1, while the present one had 92% stage IIIB of which 38% had ECOG performance status 2. Of note, the toxicity profile of the protocol was substantially better: grade 3 esophagitis 13% *versus* 32-34% grade 3-4 in the former studies.

A randomized phase II trial, using in one arm concurrent VNB+CDDP and continuous RT (60 Gy) [24], showed an OR rate of 80%, with median OS 20 months, suggesting an improved outcome following a more aggressive strategy. However, these favorable results were attained at the cost of high incidence of treatment-related toxicities (grade 3-4 neutropenia 65%, with 8% febrile neutropenia, and 18% grade 3-4 esophagitis).

It is generally agreed that, for advanced NSCLC, the quality of patients' life is an important issue of the decision making process [25]. Most of the experts consider the fact that concurrent CT+RT should be reserved for a selected category of patients because of the high rate of severe toxicity associated with this strategy [1,21]. From this perspective, our protocol could represent a suitable alternative for patients with advanced-stage disease and low performance status.

Conclusions

The results of this study show that the split course RT program with concurrent VNR and CDDP induce a low rate of treatment-related toxicity, allowing for a good DI for both RT and CT. Compared with the previous results of our institution, the efficacy of this approach seems better, and this strategy can be recommended for more advanced stages of the disease, and for patients with low ECOG performance status. More aggressive combination of CT and RT could improve the patients' outcome, but one must take into account the high rate of treatment related toxicities in this case.

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