Induction Chemotherapy Followed by Concurrent Chemoradiotherapy in Stage III Unresectable Non-small Cell Lung Cancer

Eng H. Tan, Joseph Wee, Peng T. Ang, Kam W. Fong, Swan S. Leong, Kei S. Khoo, Terence Tan, Kim S. Lee, Philip Eng, Anne Hsu, Yoke K. Tan, E.J. Chua and Yong Y. Ong

From the Departments of Medical Oncology (E.H. Tan, P.T. Ang, S.S. Leong, K.S. Khoo) and Therapeutic Radiology (J. Wee, K.W. Fong, T. Tan, K.S. Lee, E.J. Chua), National Cancer Centre, and the Department of Respiratory and Critical Care Medicine, Singapore General Hospital (P. Eng, A. Hsu, Y.K. Tan, Y.Y. Ong), Singapore

Correspondence to: Dr Eng-Huat Tan, Department of Medical Oncology, National Cancer Centre, 11 Hospital Drive, Singapore 169610, Singapore. Tel: +65 436 81 69. Fax: +65 227 27 59. E-mail: dmoteh@nccs.com.sg

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The favourable experience with the combination regimen of vinorelbine, ifosfamide and cisplatin (NIP) in patients with metastatic non-small cell lung cancer (NSCLC) has led to a protocol assessing this regimen as an induction treatment in patients with stage III unresectable NSCLC, followed by thoracic radiotherapy with concurrent daily cisplatin as a radiosensitizer. Two cycles of NIP were administered 21 days apart; each cycle comprised i.v. vinorelbine 25 mg/m^2 on days 1 and 8, i.v. ifosfamide 3 g/m^2 on day 1 with MESNA as uroprotection, and i.v. cisplatin 50 mg/m^2 on day 1. Radical thoracic radiotherapy commenced on day 43 to a total dose of 64 Gy and i.v. cisplatin 6 mg/m^2 was given concurrently prior to each fraction of radiation as a sensitiser. Two more cycles of NIP were given to patients who responded favourably to the induction treatment about 2 weeks after completion of radiation. Between July 1995 and July 1997, 44 patients were treated with this protocol. This treatment schedule was generally well tolerated. Grade 3–4 neutropenia occurred in 50% of the patients and neutropenic sepsis was seen in 8. Grade 3–4 oesophagitis was uncommon. Most of the patients were able to complete the induction and concurrent chemoradiotherapy phase. Major response occurred in 75% of the patients with 2 (4.5%) complete responses (CR). A total of 6 patients achieved CR after chemoradiotherapy. At a median follow-up of 35 months, the median overall survival for all patients was 15 months with a 3-year survival rate of 24%. The median overall survival for stage IIIA patients was 19 months with a 3-year survival rate of 39% in contrast to 13 months' median overall survival and only 15% 3-year survival rate for stage IIIB. The NIP regimen results in a high response rate in NSCLC and this treatment programme seems to benefit selected patients with stage III disease.

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There has been an increasing trend toward incorporation of chemotherapy as part of the multimodality treatment in the management of patients with unresectable stage III non-small cell lung cancer (NSCLC). Given the significant survival benefit conferred by the addition of chemotherapy to radiation, as shown in several well-conducted randomized trials, this is not surprising (1–6). The landmark paper on a meta-analysis on individual patient data from 52 randomized trials is also a contributory factor in this evolutionary change (7).

As shown in the Cancer and Leukaemia Group B (CALGB) and the intergroup studies, improvement in systemic control by the addition of chemotherapy contributed to the survival advantage (1–3). Nevertheless, systemic failure as well as local failure remains a significant problem with the old platinum-based regimens and the sequential chemotherapy-radiotherapy treatment schedule. The European Organisation for the Research and Treatment of Cancer (EORTC) study has shown that the addition of daily cisplatin concurrent with radiation in patients with locally advanced disease resulted in significantly improved survival compared with those treated with radiation alone (8). This was attributed to improved local control. Systemic control was not improved when compared to the patients treated with radiation alone. This study underscores the importance of local control in improving the survival of this group of patients.

The advent of new agents such as vinorelbine, the taxanes, and campthotecins has added significantly to the armamentarium of active agents against NSCLC. Many

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phase II studies have confirmed their activity and phase III trials for some of these agents have been reported or are underway. In particular, in a large European randomised trial the combination of vinorelbine and cisplatin has been shown to be superior to the standard regimen comprising cisplatin and vindesine in terms of response rate and survival outcome in patients with metastatic NSCLC (9).

Since 1994, we have been using a combination of vinorelbine, ifosfamide and cisplatin (NIP) for patients with metastatic/advanced NSCLC. A response rate of 58% and a 1-year survival rate of 60% were attained in 64 patients with metastatic disease treated prospectively with this regimen. Given the encouraging results, we decided to explore the use of this regimen as induction treatment in patients with unresectable stage III disease (10). We also decided to incorporate the EORTC treatment schedule of daily low-dose cisplatin concurrent with each fraction of radiation in our treatment protocol. With this, we hope to attain the dual goal of improving the systemic and locoregional control of patients with unresectable stage III NSCLC.

MATERIAL AND METHODS

Eligibility criteria

Patients must have histologically confirmed lung cancer of the non-small cell type (squamous cell carcinoma, adenocarcinoma, large cell carcinoma) obtained via bronchoscopy, or transthoracic needle biospy, or open biopsy. They must be deemed to have unresectable, locally advanced disease (stage IIIA/IIIB), good performance status of ECOG 2 or less, and have adequate renal, cardiac, hepatic, and bone marrow function. Computed scans of the brain, chest, and abdomen and bone scan were required for all patients in order to exclude systemic disease.

Treatment schedule (Fig. 1)

Each cycle of the NIP regimen (21-day cycle) was as follows: i.v. vinorelbine 25 mg/m^2 on days 1 and 8 slow bolus, i.v. ifosfamide 3 gm/m^2 on day 1 infused over 4 h with i.v. MESNA at 60% of the ifosfamide dose infused over 8 h, i.v. cisplatin 50 mg/m^2 on day 1 infused over 8 h.

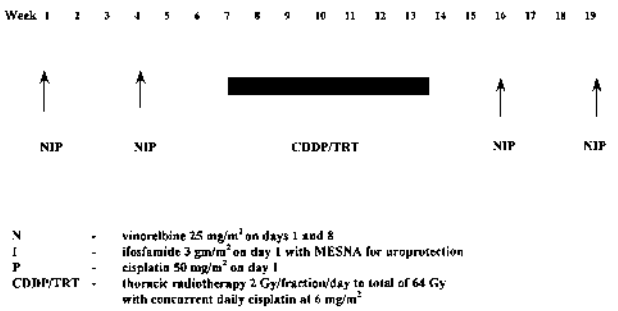

Fig. 1. Treatment schema.

A repeat CT scan of the chest was done after the second cycle, to assess response to induction treatment. Thoracic radiotherapy was commenced on day 43 and i.v. cisplatin was given concurrently with each fraction of radiation at a dose of 6 mg/m^2 as radiosensitiser. A further two cycles of NIP were given to patients who had a favourable response to induction treatment (at least a partial response, or stable radiological lesions but with significant symptomatic improvement) 2 weeks after the last fraction of radiation. A haemogram was made on days 1 and 8 of each cycle of NIP and weekly during the chemoradiotherapy phase and a serum urea/electrolytes/creatinine record was made on day 1 of each cycle of NIP and weekly during the chemoradiotherapy phase. A repeat of the CT scan was performed about 3 months from the last fraction of radiation as a final assessment of response to this treatment schedule.

Radiotherapy

Radiation therapy was started on day 43 of the treatment schedule. A total dose of 64 Gy in 32 daily fractions over six and a half weeks was delivered to the involved areas. The initial target volume included the site of the primary disease with a margin of 1.5–2 cm, the ipsilateral hilum and the whole width of the mediastinum, extending inferiorly to 4 cm below the carina. This volume received a dose of 40 Gy in 20 fractions over 4 weeks through the AP-PA portals, and was followed by oblique fields for another 10 Gy and a further field reduction treating only gross disease with a 1 cm margin through reduced oblique portals for another 14 Gy. The ipsilateral supraclavicular nodes were included only if the nodes were grossly involved or the primary disease was in the upper lobe.

Response criteria and toxicity grading

Response to treatment was assessed using standard criteria: complete response (CR) was defined as disappearance of all measurable and evaluable lesions for at least 4 weeks; partial response (PR) was a 50% reduction in the sum of perpendicular diameters of all measurable lesions lasting for at least 4 weeks; stable disease (SD) was defined as less than 25% increase in size of all lesions without appearance of new lesions; progressive disease (PD) was defined as more than 25% increase in size of all lesions or appearance of new lesions. Toxicity grading was assessed using the World Health Organization (WHO) Toxicity Criteria.

Follow-up

Patients were seen prior to each cycle of NIP and weekly during the chemoradiotherapy phase. Upon completion of treatment, they were seen once every 2 months for the first 2 years and every 3–6 monthly thereafter. Survival was calculated from the date of diagnosis and progression-free interval was dated from the day of implementation of the

Table 1

Patient characteristics

Characteristic	No.	Percentage
Age (years)		
Median	60	
Range	36–76	
Sex		
Male	36	81.8
Female	8	18.2
Stage		
IIIA	18	40.9
IIIB	26	59.1
Pathology		
Adenocarcinoma	10	22.7
Squamous	24	54.5
Large	4	9.1
Unable to subtype	6	13.6
Cycles of NIP received		
Two	11	25.0
Three	13	29.5
Four	20	45.5
Radiation dose received		
$\leq$6 000	3	6.8
>6 000	41	93.2

treatment schedule. Overall survival and progression-free survival were determined using the Kaplan–Meier method.

RESULTS

Patient characteristics (Table 1)

Between July 1995 and July 1997, 44 patients were treated with this protocol. The majority of the patients were males and 59% of the patients had stage IIIB disease. The most common histology was squamous cell carcinoma (54.5%). There was difficulty in subtyping the histology for 6 patients, but the pathologist had no difficulty in categorising them as belonging to the non-small cell group. The median age of this patient cohort was 60 years and the median number of cycles of NIP administered was 3, with 20 patients (45.5%) completing 4 cycles of NIP. Thirty-three patients (75%) were able to receive at least 80% of the intended total dose of cisplatin during radiotherapy. Forty-two patients (95.5%) completed at least 60 Gy of thoracic radiation; one patient received 50 Gy and one patient declined further treatment after 10 Gy. Radiation had to be delayed in four patients because of the toxicities.

Toxicities (Table 2)

This treatment protocol was generally well tolerated. Grade 3–4 neutropenia is the most significant haematological toxicity, occurring in 50% of the patients. However, only 8 patients experienced neutropenic sepsis. No treatment-related deaths were encountered. Oesophagitis was generally mild to moderate and posed no impediment to swallowing. Only one patient experienced grade 3 oesophagitis, requiring narcotic analgesics. The median percent body weight loss after completing the chemoradiotherapy phase was 4.4%.

Table 2

Toxicities

Toxicity	No.	Percentage
Anaemia		
Grade 0	16	36.4
Grade 1–2	27	61.4
Grade 3–4	1	2.4
Neutropenia		
Grade 0	12	27.3
Grade 1–2	10	22.7
Grade 3–4	22	50.0
Thrombocytopenia		
Grade 0	37	84.1
Grade 1–2	7	15.9
Neutropenic sepsis	8	18.2
Nausea/vomiting		
Grade 0	16	36.4
Grade 1–2	22	50.0
Grade 3	6	13.6
Oesophagitis		
Grade 1–2	43	97.7
Grade 3	1	2.3

Response to treatment (Table 3) and survival outcome

Thirty-three patients (75%) attained at least a partial response to induction NIP with 2 patients (4.5%) reaching complete response (CR). Six patients had complete responses after the chemoradiotherapy phase of treatment. At a median follow-up of 35 months, 27 patients had progression of disease; the majority had locoregional progression but only 10 patients had systemic failure. The median progression-free survival (MPFS) of all patients was 10 months and the 3-year progression-free survival (PFS) was 12% (Fig. 2). The MPFS and 3-year PFS for stage IIIA were 11 months and 20%, respectively, in contrast to the respective figures of 9 months and 10% for stage IIIB (Fig. 3). The median overall survival (MOS) for all patients was 15 months and 24% of the patients were

Table 3

Response to induction NIP

Response	No.	Percentage
Partial	31	70.5
Complete	2	4.5
Overall	33	75.0
Stable	9	20.5
Not evaluable	2	4.5

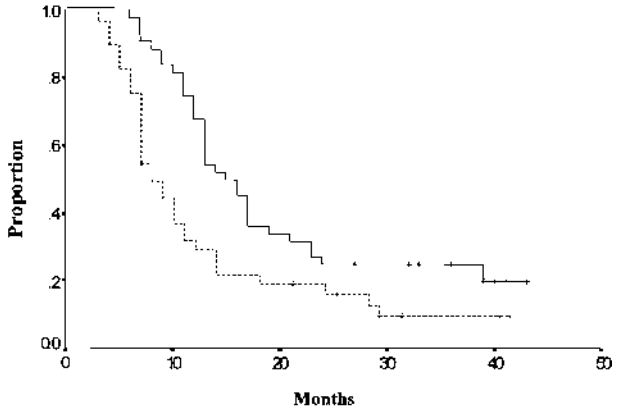

Fig. 2. Overall and progression-free survival for all patients. — = Overall survival; . . . . . = progression-free survival.

alive at 3 years (Fig. 2). For stage IIIA patients, MOS was 19 months and 39% of them were alive at 3 years. Stage IIIB patients, however, did not fare well, with a MOS of 13 months and 15% 3-year survival (Fig. 4). In particular, none of those with scalene nodal disease attained long-term disease control and survival.

DISCUSSION

Radiotherapy alone has been the traditional treatment of choice for patients with unresectable stage III NSCLC. However, recent data from various randomised trials have established a role for chemotherapy for this group of patients. The sequential use of induction chemotherapy followed by radiotherapy is the only established way of using these two modalities of treatment. However, the result of treatment with this sequencing schedule, though significantly better than radiation alone, is far from satisfactory. Most of these patients (about 80%) will be expected to die from their disease within 5 years.

We have incorporated both sequential and concurrent chemotherapy with thoracic radiotherapy in our study.

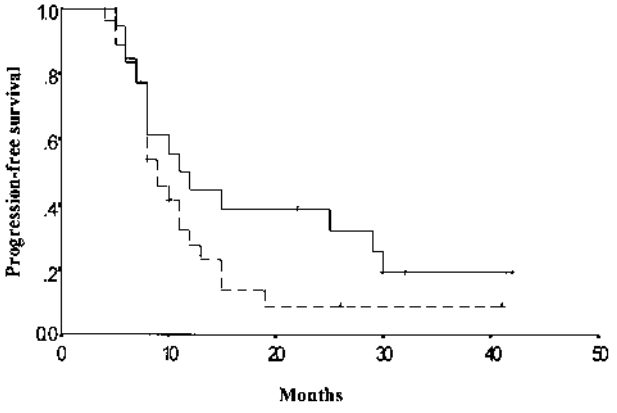

Fig. 3. Progression-free survival according to stage. — = Stage IIIA; ---- = Stage IIIB.

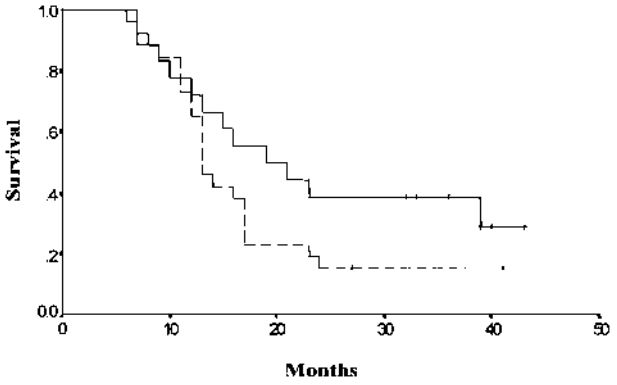

Fig. 4. Overall survival according to stage. — = Stage IIIA; ---- = Stage IIIB.

Although this treatment schedule is shown to be well tolerated by most patients and is generally safe, it clearly does not benefit a certain subset of patients. Proper patient selection is still important for this form of treatment programme.

Systemic control with NIP seemed to be quite promising and this is in line with the high response rate noted with this regimen. While daily low-dose cisplatin with radiation was well tolerated, it did not have a sufficiently radiosensitising effect. Locoregional failure is still a problem. Theoretically, the addition of surgery in a triple modality treatment programme could benefit these patients. Another method that can potentially improve locoregional control is the use of combination chemotherapy regimens concurrently with radiation.

The optimal sequencing of chemotherapy and radiotherapy has yet to be determined. How surgery can be incorporated into the treatment schedule in this group of patients with otherwise unresectable disease should also be investigated. The scope for future research work is tremendous. Much effort will be required.

REFERENCES

1. Dillman RO, Seagren SL, Propert KJ, et al. A randomised trial of induction chemotherapy plus high dose radiation versus radiation alone in stage III non-small cell lung cancer. N Engl J Med 1990; 323: 940–5.
2. Dillman RO, Seagren SL, Herndon J, et al. Randomised trial of induction chemotherapy + radiation therapy versus radiation therapy alone in stage III non-small cell lung cancer. Five-year follow-up of CALGB. Proc Am Soc Clin Oncol 1993; 12 (Abstr 1092): 329.
3. Sause WT, Scott C, Taylor S, et al. Radiation Therapy Oncology Group (RTOG) 88-08 and Eastern Cooperative Oncology Group (ECOG) 4588: preliminary results of a phase III trial in regionally advanced, unresectable non-small cell lung cancer. J Natl Cancer Inst 1995; 87: 198–205.
4. Le Chevalier T, Arriagada R, Quoix E, et al. Radiotherapy alone versus combined chemotherapy and radiotherapy in non-resectable non-small cell lung cancer: first analysis of a randomised trial in 353 patients. J Natl Cancer Inst 1991; 83: 417–23.

5. Le Chevalier T, Arriagada R, Tarayre M, et al. Correspondence—Significant effect of adjuvant chemotherapy on survival in locally advanced non-small cell lung cancer. J Natl Cancer Inst 1992; 84: 58 (letter).
6. Wolf M, Hans K, Becker H, et al. Radiotherapy alone versus chemotherapy with ifosfamide/vindesine followed by radiotherapy in unresectable locally advanced non-small cell lung cancer. Semin Oncol 1994; 21 (Suppl 4): 42–7.
7. Non-small Cell Lung Cancer Collaborative Group. Chemotherapy in non-small cell lung cancer: a meta-analysis using updated data on individual patients from 52 randomised clinical trials. Br Med J 1995; 311: 899–909.
8. Schaake-Koning C, Bogaert WVD, Dalesio O, et al. Effects of concomitant cisplatin and radiotherapy on inoperable non-small cell lung cancer. N Engl J Med 1992; 326: 524–30.
9. Le Chevalier T, Pujol JL, Douillard JY, et al. A three-arm trial of vinorelbine (Navelbine) plus cisplatin, vindesine plus cisplatin, and single agent vinorelbine in the treatment of non-small cell lung cancer: an expanded analysis. Semin Oncol 1994; 21 (Suppl 1): 28–33.
10. Tan EH, Ang PT, Wee J, et al. Vinorelbine, ifosfamide and cisplatin in advanced non-small cell lung cancer. Acta Oncol 1999; 38: 619–22.