Clinical Trials Notes

Feasibility Of Administering Adjuvant Chemotherapy Of Pemetrexed Followed By Pemetrexed/oxaliplatin Immediately Post –VATS In Patients With Completely Resected NSCLC

Jianxing He, MD, PhD, FACS, Wenlong Shao, MD, Shuben Li, MD, Manyin Chen, MD, Hanzhang Chen, MD, Jun Liu, MD, Wei Wang, MD, Yuan Qiu, MD, and Daoyuan Wang, MD

From Department of Cardiothoracic Surgery, the First Affiliated Hospital of Guangzhou Medical College; Guangzhou Research Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease, Guangzhou, PR China

ABSTRACT Non-small cell lung cancer (NSCLC) accounts for the largest number of cancer deaths annually, worldwide. It seems reasonable to test a less toxic regimen also in early stages after complete (R0) resection of the tumor, where reduced toxicities might improve the feasibility of drug delivery, compliance and the convenience of treatment for the patient and hence perhaps improve survival. The main purpose of this phase II trial is to evaluate the clinical feasibility-in terms of patients without dose limiting toxicities or premature treatment withdrawal or death-of administering adjuvant chemotherapy of pemetrexed followed by pemetrexed/oxaliplatin immediately post-VATS (video-assisted thoracic surgery) in patients with completely resected NSCLC.

KeyWords: non-small cell lung cancer; video-assisted thoracic surgery; adjuvant chemotherapy; pemetrexed; oxaliplatin

J Thorac Dis 2009; 1: 55–62.

1. Introduction

Non-small cell lung cancer (NSCLC) accounts for the largest number of cancer deaths annually, worldwide (1). Of these, about 30% are early stage patients (stage I and II). For this group of patients, radical surgery with mediastinal lymph node dissection has been the mainstay of therapy with a reasonable curative option. However, 5-year survival rates for patients with pathologically staged IA-IIB disease are ranging from 67% to 39% (2). Following surgery, distant recurrence is the most common form of relapse and eventual cause of death. Assuming that these recurrences are due to occult micrometastases at the time of surgery, trials on adjuvant systemic therapy have been performed in an attempt to reduce the risk of recurrence and to improve survival.

In some of the recently published trials a clear benefit of adjuvant chemotherapy in early stage NSCLC could not be achieved (3-5). In marked contrast to these studies, three recent, big randomized trials on early stage NSCLC patients with modern platin-based two-drug chemotherapy-regimens revealed a significant advantage for overall or relapse free survival for chemotherapeutically treated patients (6-8). The majority of patients in the adjuvant treatment setting received a combination of cisplatin and vinorelbine. A pooled analysis of five big randomized studies demonstrated that adjuvant cisplatin-based chemotherapy significantly improves survival in patients with NSCLC (overall HR of death 0.89, P=0.005) corresponding to a 5-year absolute benefit of 5.4% from chemotherapy (9). However, toxicity and inadequate dose delivery have been critical issues in all trials performed so far. Grade 3/4 toxicities are observed up to 73% with rates of neutropenic fever up to 7%. Up to 77% of the patients had at least one dose reduction or omission and 55% required one dose delay or more, most related to neutropenia (7, 10).

There are few data in the literature about how soon after surgery a patient begins adjuvant chemotherapy, although most trials seem to start after a post-surgical interval of 4-6 weeks. A recent study reported that 26 patients, who underwent thoracoscopic (video-assisted thoracic surgery, VATS) lobectomy, receiving chemotherapy, 73% completed a full course on schedule and 85% received all intended cycles (11). In another study, complete resection was performed by thoracotomy in 43 patients and by thoracoscopy in 57 patients, compared with thoracotomy, patients undergoing thoraco scopic lobectomy had significantly fewer delayed (18% versus 58%, P < 0.001) and reduced (26% versus 49%, P = 0.02) chemotherapy doses. A higher percentage of patients undergoing thoracoscopic resection received 75% or more of their planned adjuvant regimen without delayed or reduced doses (61% versus

The authors have no commercial, proprietary, or financial interest in the products or companies described in this article.

Corresponding author: Prof. Dr. Jianxing He, MD, PhD, FACS. Department of Cardiothoracic Surgery, The First Affiliated Hospital of Guangzhou Medical College; Guangzhou Research Institute of Respiratory Disease & China State Key Laboratory of Respiratory Disease. No. 151, Yanjiang Rd, Guangzhou 510120, PR China. Tel:+86-20-83337792, Fax: +86-20-83350363, Email: hejx@vip.163.com

ISSN: 2072-1439/$ - see front matter

40%, P = 0.03). There were no significant differences in time to initiation of chemotherapy or toxicity (12). In comparison, the Cancer and Leukemia Group B trial 9633 reported that 57% of patients received full-dose chemotherapy (13) and the Intergroup JBR.10 trial reported that 55% of patients had at least 1 dose delay (7). Approximately 34% of patients in the Adjuvant Lung Project Italy series chemotherapy wing received all scheduled doses without adjustment or delay; 69% completed their treatments with or without adjustments or delay (4). It is conceivable that patients who undergo VATS may have a quicker recovery and in general more strength to tolerate chemotherapy. There are theoretic survival benefits to starting chemotherapy immediately after surgery because the body's tumor burden should be lowest, and tumor growth fastest, at this time. Thus, chemotherapy administered immediately post-surgery would be most effective, assuming that wound healing is adequate (11).

Pemetrexed, a multi-target folate antimetabolite, shows clear activity in non-small cell lung cancer. In a phase III study for patients with previously treated advanced non-small cell lung cancer, the efficacy of single-agent pemetrexed, as determined by overall survival, was similar to that of docetaxel (14). The combination of oxaliplatin and pemetrexed has been of particular interest because it has demonstrated both good efficacy and a tolerable side effect profile. Oxaliplatin is a diaminocyclohexane-containing platinum compound that inhibits DNA replication and transcription by forming DNA adducts. Its mechanism of action is similar to that of the classic platinum drugs, but molecular pharmacology studies suggest that oxaliplatin represents a distinct family of platinum compounds. It has a different cytotoxicity profile from cisplatin and can be safely given in the outpatient setting without hydration therapy (15). Moreover, oxaliplatin appears to interact synergistically with pemetrexed (16). Phase I studies evaluated pemetrexed plus oxaliplatin in patients with solid tumors, and showed the regimen was efficacious and well tolerated (17). The combination of oxaliplatin and pemetrexed was compared with carboplatin and pemetrexed as first-line therapy for advanced NSCLC in a randomized phase II study. Response rates were 26.8 and 31.6%, respectively, and not statistically different. However, toxicity in the oxaliplatin/pemetrexed arm was quite low, this doublet can be delivered easily and is well tolerated. Furthermore, it results in a 7.3% rate of grade 3/4 neutropenia only and the incidence of febrile neutropenia was 2.4%. Dose reductions occur only in 2.6% cycles. Patients received 95.3% and 100% of the planned weekly mean doses of pemetrexed and oxaliplatin, respectively (18).

Therefore, it seems reasonable to test a less toxic regimen also in early stages after complete (R0) resection of the tumor, where reduced toxicities might improve the feasibility of drug delivery, compliance and the convenience of treatment for the patient and hence perhaps improve survival. The main purpose of this phase II trial is to evaluate the clinical feasibility-in terms of patients without dose limiting toxicities or premature treatment withdrawal or death-of administering adjuvant chemotherapy of pemetrexed followed by pemetrexed/oxaliplatin immediately post-VATS in patients with completely resected NSCLC.

2. Objectives and Outcome Measures

2.1 Primary Outcome Measures:

This study is a prospective phase II study determining the clinical feasibility in terms of toxicity of 4 cycles of adjuvant chemotherapy with pemetrexed followed by pemetrexed/oxaliplatin in patients with completely resected non-squamous NSCLC (stage IB, IIA, IIB and IIIA) by VATS, after a postersurgical interval of 2-4 weeks, to estimate whether patients who undergo VATS may have a quicker recovery and in general more strength to tolerate chemotherapy.

The primary objective is to determine the clinical feasibility rate (CFR) of 4 cycles of adjuvant chemotherapy with pemetrexed followed by pemetrexed/oxaliplatin in patients with NSCLC stage IB, IIA, IIB and IIIA after a postersurgical interval of 2-4 weeks. Treatment is considered to have clinical feasibility if dose limiting toxicity (DLT) will not be observed, and no non-acceptance by the patient leading to premature withdrawal, and no death due to cancer or cancer therapy will occur.

DLTs are defined as:

- Grade 4 neutropenia more than 7 days
- Grade 4 thrombocytopenia more than 7 days
- Grade 3/4 neutropenia with fever (i.e. > 38.5° C on at least 2 occasions in 24 hours time) and/or infection (i.e. documented by either culture or imaging method)
- Any grade thrombocytopenia with bleeding
- Grade 3/4 non-hematological toxicity possibly or probably related to the chemotherapy (except for nausea/vomiting/hair loss)

2.2 Secondary Outcome Measures:

Secondary objectives are to determine the time to treatment failure, the relapse free survival, the overall survival, the distant metastases free survival, local relapse free survival, the localization of relapse.

3. Statistical Consideration

This phase II trial design is based on the following assumptions: the experimental therapy arm would be rated as unacceptable, if the actual feasibility rate (= 1 withdrawal/DLT rate) was 65 % or lower. On the other hand, the therapy would be considered to be a promising candidate for further development, if the true feasibility rate amounted to 80% or more. Probability to accept the experimental therapy as well tolerable, in spite of a true feasibility rate of < 65% (i.e. withdrawal/DLT rate > 35%): 5% (type I error). Probability to reject the experimental therapy as not sufficiently feasible (< 65%), although the true feasibility rate is promising (> 80%):

20% (type II error, corresponding to a power of 80%). According to these parameters, and using the variant out of the class of optimal two-stage designs by Simon that leads to the lowest maximum number of patients required (minimax approach), n = 18 patients evaluable for feasibility have to be recruited in the first stage (19). The combination will be rejected, if three or more of these patients fulfil the criterion of non-feasibility. In the second step, further patients will be recruited up to a total number of 67 cases. Allowing for a follow-up loss rate of 10%, the total sample size was 75 patients.

The final conclusion of the trial will depend on the definite feasibility rate (and its confidence interval), the achieved level of drug delivery as well as the complete information on type, frequency and severity of toxicities. Event related data like relapse-free or overall survival will be estimated by the product limit method by KAPLAN-MEIER CURVE and compared using the log-rank test. The methods mentioned above are likewise suitable for the univariate evaluation of prognostic factors. Multivariate analyses may be performed by suitable regression models (COX proportional hazard regression model, logistic regression).

4. Patient Selection

4.1 Inclusion Criteria:

Patients are eligible to be included in the study only if they meet all of the following criteria:

- Patients with completely resected stage IB (>4 cm), II, or IIIA non-squamous NSCLC by VATS. Patient must be enrolled and begin therapy within 4 weeks from the date of complete surgical resection.
- Fresh tissue must be available for genomics expression profiling.
- ECOG performance status of 0 or 1.
- No prior chemotherapy, radiation therapy, or biologic/targeted therapy within the last 5 years. Prior therapy with low dose methotrexate or similar medications is allowed if therapy used to treat non-malignant conditions.
- Age ≥ 18 years.
- No previous or concomitant malignancy in the past 5 years other than curatively-treated carcinoma in situ of the cervix, or basal cell or squamous cell carcinoma of the skin.
- No other serious medical or psychiatric illness.
- Signed informed consent.
- Required laboratory data within one week of enrollment:
  - *ANC or AGC ⩾ 1500 per uL;*
  - *Platelets ⩾ 100,000 per uL;*
  - *Total bilirubin ⩽ 1.5 mg/dL;*
  - *Creatinine < 2 mg/dL; creatinine clearance ⩾ 45 mL/min;*
  - *SGOT/SGPT ⩽ 1.5× ULN.*
- Females of child-bearing potential (not surgically sterilized and between menarche and 1 year post menopause) must test negative for pregnancy within 7 days prior to or at the time of enrollment based on a serum pregnancy test. Both sexually active males and females of reproductive potential must agree to use a reliable method of birth control, as determined by the patient and their health care team, during the study and for 3 months following the last dose of study drug.

4.2 Exclusion Criteria:

Patients will be excluded from the study if they meet any of the following criteria:

- Treatment within the last 30 days with a drug that has not received regulatory approval for any indication at the time of study entry.
- Concurrent administration of any other anti-tumor therapy.
- Inability to comply with protocol or study procedures.
- Active infection requiring IV antibiotics, antifungal or antiviral agents, that in the opinion of the investigator would compromise the patient's ability to tolerate therapy.
- Major surgery (other than definitive lung cancer surgery) within two weeks of study or other serious concomitant systemic disorders that, in the opinion of the investigator, would compromise the safety of the patient or compromise the patient's ability to complete the study.
- Myocardial infarction having occurred less than 6 months before inclusion, any known uncontrolled arrhythmia, symptomatic angina pectoris, active ischemia, or cardiac failure not controlled by medications.
- Contraindication to corticosteroids.
- Inability or unwillingness to take folic acid or vitamin B12 supplementation.
- Unwillingness to stop taking herbal supplements while on study.
- Presence of clinically significant third-space fluid collections (for example, ascites or pleural effusions) that cannot be controlled by drainage or other procedures prior to study entry and throughout study enrollment as the distribution of pemetrexed in this fluid space is not fully understood.
- Inability to discontinue administration of aspirin at a dose > 1300 mg/day or other long acting, non-steroidal anti-inflammatory agents for 2 days before, the day of, and 2 days after the dose of pemetrexed (5 days prior for long-acting agents such as piroxicam). Moderate dose ibuprofen may be continued.
- Female patients that are pregnant or breast-feeding.

5. Pretreatment Evaluation

The following assessments will be performed before, during and after the study (Table 1). Optimal preoperative staging should have consisted of the following procedures and should have been assured at least in a time interval starting 7 days prior to surgery: CT scan of the thorax and abdomen including adrenal glands and the

Table 1 Flow chart study procedures

	Pre-study Phase		Adjuvant Chemotherapy Phase				1st follow up	Further Follow-Up
			Cycle 1	Cycle 2	Cycle 3	Cycle 4		
Timeframe(days)	-7 prior to Surgery	-7 prior to Chemotherapy start	1-21	22-42	43-63	64-84	114	Untile 3 years after CTX
Day of visit	-7 prior to Surgery	-7 prior to Chemotherapy start	1	22	43	64	114	startin g 3 month after 1st follow up in Years 1 & 2: 3-monthly, then 6-monthly
Informed Consent		X						
Demography		X						
Pregnancy test		X[1]						
Medical history, Signs and symptoms		X						
Neurological Status		X	X	X	X	X		
Clinical Examination		X[2]	X[2]	X[2]	X[2]	X[2]	X[2]	X[2]
Concomitant medication		X	X	X	X	X	X	X
Laboratory hematology		X	X[3,4]	X[3,4]	X[3,4]	X[3,4]	X	X
Laboratory hepatic		X	X[4]	X[4]	X[4]	X[4]	X	X
Laboratory renal		X	X[4]	X[4]	X[4]	X[4]		
Laboratory electrolytes		X	X[4]	X[4]	X[4]	X[4]		
Laboratory coagulation		X						
12-lead ECG		X						
Assessment of LVEF[9]		X						
Chest-X-ray		X					X[5]	X[5]
Abdomen ultrasound	X[6]						X[10]	X[10]
MRT or CT skull	X							
CT lower liver marginliver[6]	X							
Assessment of vital/total capacity		X					X	
Assessment of FEV1		X					X	
Assessment of absolute DLCO or BGA under resting conditions		X					X	
Bone Scintigraphy[7]	X							
Audiometry[8]		X						
Compliance		X	X	X	X	X		
Adverse events		X	X	X	X	X	X	X
Follow-Up tumor assessment[5]		X					X	

[1]in women with child–bearing potential; [2]Clinical examination including physical examination, neurologic assessment, height (height only to be assessed at baseline), weight, vital signs, Karnofsky or ECOG Performance Status at the beginning of each chemotherapy cycle; [3]hematology parameters, including Hb, platelets, WBC, ANC at least once weekly during chemotherapy phase; [4]Three days prior to or at least at day 1 of each chemotherapy–cycle; [5]Relapse of disease should be confirmed by imaging techniques; [6]CT scan of the thorax and abdomen including adrenal glands and the right lower liver margin (in case adrenal glands are not available further CT scan of the abdomen is mandatory; if only right lower liver margin is not available assessment by either CT scan of abdomen or abdominal ultrasound should be performed); [7]If a FDG–PET scan has been performed, bone scintigraphy can be omitted; [8]Optional; patients with clinical suspicion of altered hearing capability or symptoms should undergo further evaluation by audiometry; [9]Echocardiography optional, mandatory only in case of doubt whether cardiac function allows Cisplatin chemotherapy; 10optional, left to the discretion of the center prior to study initiation of the center

right lower liver margin (in case adrenal glands are not available further CT scan of the abdomen is mandatory; if only right lower liver margin is not available assessment by either CT scan of abdomen or abdominal ultrasound should be performed), MRT (preferably) or CT scan of the skull and bone scintigraphy (if a FDG-PET scan has been performed bone scintigraphy can be omitted).

Not more than 7 days prior to the start of chemotherapy, for all patients the following baseline parameters will be assessed: patient demography, clinical examination including physical examination, height, weight, vital signs, ECOG Performance Status, assessment of the neurological status, existing signs and symptoms, medical history (including concurrent illnesses) and specific details on the diagnosis of non-small cell lung cancer (NSCLC), previous anti-cancer therapy and their outcome, concomitant medication, laboratory assessment including hematological parameters (hemoglobin, WBC, ANC, platelets), electrolytes (Na, K, Ca), hepatic parameters (total bilirubin, ASAT, ALAT, AP, gGT, LDH), renal parameters (creatinine, calculated creatinine clearance, Urea, uric acid), coagulation parameters (Quick, PTT, Fibrinogen), and pregnancy test for women with childbearing potential. Furthermore chest-X-ray, electrocardiography and optional echocardiograph will be performed.

Pulmonary function will be assessed by FEV1, vital capacity and total capacity and by either absolute DLCO or capillary/arterial BGA in resting condition with absolute DLCO > 40 % or pO2 > 60 mmHg in resting condition. Patients with clinical suspicion of altered hearing capability or symptoms, e.g. tinnitus, should undergo further evaluation by audiometry. If preoperative staging had not comprised all mandatory procedures it should be completed as outlined above before registration.

6. Registration Procedures

The current phase II trial is a single institution study. All patients should be seen by principle investigator (Dr Jianxing He, MD, PhD, FACS), and should be registered in the Department of Cardiothoracic Surgery, Guangzhou Research Institute of Respiratory Disease, China State Key Laboratory of Respiratory Disease, the First Affiliated Hospital of Guangzhou Medical College.

Every patient must provide a written informed consent to the trial procedures. The patient must be informed verbally and by the provided patient information by the investigator before informed consent is obtained.

7. Chemotherapy

In the first cycle, patients received Pemetrexed 500 mg/m^2 (i.v. infusion over 10 minutes) on day 1 of a 21-day cycle. From 2nd cycle, patients received pemetrexed 500 mg/m^2 (i.v. infusion over 10 minutes) then oxaliplatin 120 mg/m^2 (i.v. infusion over 120 minutes) on day 1 of a 21-day cycle. Study drug administration is to begin on d14 to d28 after R0 resection of the tumor. A total of three cycles is intended for patients with stage IB NSCLC, and four cycles for II-IIIA NSCLC, respectively.

Folic acid (350-1000 μg) must be given daily beginning approximately 5-7 days prior to first dose of pemetrexed and continuing daily until 3 weeks after the last dose of study therapy. Vitamin B12 (1000 μg) will be administered as an intramuscular injection approximately 1 to 2 weeks prior to first dose of pemetrexed and repeated approximately every 9 weeks until 3 weeks after the last dose of study therapy. Dexamethasone (4 mg of oral or equivalent) given twice daily should be taken on the day before, the day of, and the day after each dose of pemetrexed, for rash prophylaxis unless medically contraindicated.

8. Toxicity management

Toxicities are classified by grade, type, duration, onset, and relationship to study treatment according to CTCAE version 3.0. After application of chemotherapy blood count should be performed at least once weekly. In case of leukocytopenia or neutrocytopenia CTC grade 4 (leukocytes < 1.0× 10^9/L), antibiotic prophylaxis according to local habits is recommended. Prophylaxis should be used similarly in both treatment arms. Routine use of colony-stimulating factor (CSF) is not permitted during this study. ASCO guidelines for use of CSF should be followed (20). Granulocyte colony stimulating factor must have been discontinued at least 24 hours prior to the start of the next chemotherapy infusion. In case of thrombocytopenia CTC grade 4 the patient will be discontinued from the study. In the event of CTC Grade 3 or 4 diarrhea, the following supportive measures are allowed: hydration, octreotide, and antidiarrheals. If diarrhea is severe (requiring intravenous rehydration) and/or associated with fever or severe neutropenia (Grade 3 or 4), broad-spectrum antibiotics must be prescribed. Patients with severe diarrhea or any diarrhea associated with severe nausea or vomiting must be hospitalized for intravenous hydration and correction of electrolyte imbalances. Patients with CTC grade 3 or 4 diarrhea will be discontinued from the study. Professional supervised oral care protocols that include patient education in an attempt to reduce the severity of mucositis from chemotherapy is highly advised to all patients. In case of mucositis related pain, symptomatic therapy according to WHO guidelines should be performed. Based on their proposed mechanisms, antimicrobial agents, such as combined polymyxin E, tobramycin, and amphotericin or single-agent iseganan, appear to have no associated mechanistic rationale for the prevention of mucositis and probably could provide benefit only for patients with late-stage ulcerative mucositis, in which bacterial superinfection occurs. The use of amphotericin suspension at clinical signs of mucosal soor and at mucositis Grad 3/4 is recommended. For patients receiving pemetrexed leucovorin should be considered. Patients with CTC grade 3 or 4 mucositis will be discontinued from the study.

9. Dose adjustments, safety and discontinuation of treatment

The dose reductions are limited to a preset pattern, and eliminate the need to make any calculations or resolve conflicting recommendations if two or more toxicities occur within the same cycle. It also ensures that therapeutic chemotherapy doses will be administered in all treatment cycles. Patients should be instructed to report any toxicity that occurs during drug administration of each treatment course and in the period between cycles. Treatment will be modified in case of hematological and/or non-hematological toxicities. All dose adjustments will be made according to the system showing the greatest degree of toxicities. Toxicities will be graded according to the NCI Common Toxicity criteria (CTCAE version 3.0). No dose re-escalation will be performed after dose reduction. If the study treatment cannot be administered after an additional 2 weeks delay because of any toxicity, it should be definitively discontinued.

On day 1 of each cycle, the following criteria have to be met for the administration of pemetrexed or oxaliplatin/pemetrexed: ANC = 1,500/μl, Platelets = 100,000/μl, Serum creatinine < 1.5 mg/dl and calculated creatinine clearance = 60 ml/min, no other grade = 2 toxicity (except for clinically non-relevant AEs such as alopecia, altered taste, nausea, vomiting). If these criteria are not met, drug administration has to be delayed up to 1 week to allow for recovery. If a delay of more than 14 days due to toxicity is necessary, the patient is to be discontinued from the study.

Dose adjustments according to hematological toxicity at the start of a subsequent course of the therapy will be based on platelet and neutrophil nadir counts from the preceding cycle of therapy. No dose modifications will be made for anemia. ANC must be = 1,500/μ l and platelets =100,000/μ l as outlined above prior to the start of any cycle. Treatment may be delayed to allow sufficient time for recovery. Upon recovery patients should be re-treated using the guidelines as outlined in table 2.

Table 2
Dose modifications according to hematological toxicity in previous cycle

Platelets (× 10^9/L) Nadir	ANC (× 10^9/L) Nadir	Percent or previous dose (both drugs)
≥ 50 and	≥ 0.5	100 %
≥ 50 and	< 0.5	75%
< 50 and	Any	50%
Any and	< 1.0 + fever of = 38.5° C[a]	75%
Recurrence of CTC Grade 3 or 4 after 2 dose reductions	Recurrence of CTC Grade 3 or 4 after 2 dose reductions	Discontinue patient from study

[a]these criteria meet the CTCAE version 3.0 (NCI 2003) definition of febrile neutropenia

Any patient experiencing Grade 3/4 non-hematological toxicity (except for nausea/vomiting/hair loss) associated with therapy will be discontinued from the study. In case of neurological and/or hearing CTC grade 2 toxicity, administration should be delayed and reassessed one week later. If toxicity has resolved at least to grade 1 therapy should be continued with 50% dose reduction for oxaliplatin for further administrations. In case of decrease of calculated creatinine clearance, despite adequate hydration, administration has to be delayed and reassessed one week later and if the value of creatinine clearance remains < 60 ml/min, patient has to be discontinued.

For patients who develop clinically significant pleural or peritoneal effusions (on the basis of symptoms or clinical examination) during therapy, consideration should be given to drain the effusion prior to therapy. Though, if, in the investigator's opinion, the effusion represents relapse and/or progression of disease, the patient should be discontinued from study therapy. However, disease relapse has to be confirmed by adequate imaging methods. Patients with sero (pneumo)-thorax after hemi-pneumonectomy or lobectomy will not be excluded. Those patients must be monitored for toxicity closely.

Dose reductions for hepatic dysfunction will be based on bilirubine and/or transaminase values. For bilirubin values 1.5-3 × UNL and ASAT/ALAT < 5 × UNL, vinorelbine has to be reduced to 50%. For Grade 3/4 hepatic toxicity the patient has to be discontinued from study.

10. Premature withdrawal

Patients have the right to withdraw from the study at any time for any reason. The investigator also has the right to withdraw patients from the study in the event of intercurrent illness, adverse events, protocol violations, administrative reasons or other reasons. Discontinuation of a patient should be based upon one of the objective toxicity criteria. The following reasons can lead to premature withdrawal from therapy of a patient: major protocol violation, Non-compliance of a patient with protocol procedures, unacceptable toxicity according to the protocol, unacceptable toxicity as perceived by the patient (refusal to continue), withdrawal of consent by the patient, lost to follow-up, pregnancy, medical decision

by the investigator, appropriate evaluation demonstrates recurrence of disease. The reason for withdrawal of a patient needs to be documented. Patients who have been withdrawn from therapy will have to be further documented for follow-up.

11. VATS

VATS will be performed prior to chemotherapy. The surgical principles follow the guidelines of oncologic surgery. The tumor and all intrapulmonary lymphatic drainage must be removed completely, employing lobectomy or pneumonectomy or complex resections, if necessary. En bloc resection of closely adjacent or invaded structures is preferential to a discontinuous resection. Resection margins should be assessed by frozen section analysis whenever possible; this includes bronchial, vascular and other margins with close proximity to the tumor if necessary to obtain radical resection. Re-excision is preferred whenever possible, if positive resection margins are encountered. To achieve uncomplicated bronchus- and trachealhealing stump or anastomoses (sleeve resection) can be covered with viable tissue (pedicled pleural, pericardial, intercostals muscle flap or others). Considering the criteria of functional operability, the aim is to obtain R0-resection. All accessible hilar and mediastinal lymph nodes should be removed for pathologic evaluation, using the technique of mediastinal lymph node dissection.

The systematic nodal dissection (SND) will be performed in a standardized manner same as the previous report (21, 22). All the surrounding fat containing the lymph tissue is isolated and removed systematically. Lymph nodes are to be identified and properly labelled by the surgeon. Tumor infiltration of lymph nodes may not be apparent and is recommended to be diligently sought. Microscopic assessment is required to accurately determine the N-status and should be performed as described in the previous report (23). Complete mediastinal lymph node dissection is defined as when all tissue containing lymph nodes is removed at all levels accessible within the operation. Reflecting lymph node involvement, R0-resection is defined by the absence of tumor infiltration in the most distal lymph node level removed according to the previous report (24). If possible, the most distant level should be the upper-paratracheal lymph nodes (Level 2). The natural course of a developing sero (pneumo)-thorax in case of pneumonectomy or lobectomy is not regarded as a exclusion criteria. However, patients must be followed up closely for developing toxicities.

12. Radiotherapy

Radiotherapy is not planned.

13. Maintenance Therapy and Follow Up Period

No maintenance therapy is allowed. Follow-up visits are planned starting at 30 days after the end of the last chemotherapy cycle and afterwards in 3 monthly intervals for the first 2 years. In the 3rd year patients will be followed up in 6 monthly intervals (Table 1). The follow up visits comprise clinical examination including physical examination, neurologic assessment, weight, vital signs, ECOG Performance Status, laboratory assessment including hematological parameters (hemoglobin, WBC, ANC, platelets), hepatic parameters (total bilirubin, ASAT, ALAT, AP, LDH), chest X-ray, with further examinations in case of clinical symptoms, to confirm relapse by imaging techniques, abdominal ultrasound, concomitant medication. Additional assessments in the 1st follow up at 30 days after the end of the last chemotherapy cycle comprise assessment of FEV, of vital and total capacity, capillary or arterial BGA under resting conditions, absolute DLCO and adverse events. Further examinations in case of clinical symptoms to confirm relapse by imaging techniques.

14. Trial duration

Individual participation is completed either three years after enrolment or death of the patient. Duration of the study is about 4 years.

15. Pathology

Pathology specimen (fresh tissue or paraffin block) is not needed for testing in the current study. However, efforts should be made to retain fresh tissues for gene profiling in the future against the treatment outcome for the potential identification of the gene signature that may predict the treatment outcome and patients'prognoses.

16. Data Collection

All finding on weekly or follow-up examination are to be entered to the patient data sheet specific for this study, and the database collectively controlled by Dr Jianxing He, MD, FACS.

17. ClinicalTrials.gov Registration

This study protocol was registered in the ClinicalTrials.gov (NCT00923637), a service of the United States National Institute of Health, on June 17, 2009.
(http://clinicaltrials.gov/ct2/show/NCT00923637)

Reference

1. Ferlay J, Autier P, Boniol M, Heanue M, Colombet M, Boyle P. Estimates of the cancer incidence and mortality in Europe in 2006. Ann Oncol 2007;18:581-92.
2. Mountain CF. Revisions in the International System for Staging Lung Cancer. Chest 1997;111:1710-7.
3. Tada H, Tsuchiya R, Ichinose Y, Koike T, Nishizawa N, Nagai K, Kato H. A randomized trial comparing adjuvant chemotherapy versus surgery alone for completely resected pN2 non-small cell lung cancer (JCOG9304). Lung Cancer 2004; 43:167-73.

4. Scagliotti GV, Fossati R, Torri V, Crinò L, Giaccone G, Silvano G, et al; Adjuvant Lung Project Italy/European Organisation for Research Treatment of Cancer-Lung Cancer Cooperative Group Investigators.Randomized study of adjuvant chemotherapy for completely resected stage I, II, or IIIA non-small-cell Lung cancer. J Natl Cancer Inst 2003;95:1453-61.
5. Waller D, Peake MD, Stephens RJ, Gower NH, Milroy R, Parmar MK, et al. Chemotherapy for patients with non-small cell lung cancer: the surgical setting of the Big Lung Trial. Eur J Cardiothorac Surg 2004;26:173-82.
6. Arriagada R, Bergman B, Dunant A, Le Chevalier T, Pignon JP, Vansteenkiste J; International Adjuvant Lung Cancer Trial Collaborative Group. Cisplatin-based adjuvant chemotherapy in patients with completely resected non-small-cell lung cancer. N Engl J Med 2004;350:351-60.
7. Winton T, Livingston R, Johnson D, Rigas J, Johnston M, Butts C, et al; National Cancer Institute of Canada Clinical Trials Group; National Cancer Institute of the United States Intergroup JBR.10 Trial Investigators. Vinorelbine plus cisplatin vs. observation in resected non-small-cell lung cancer. N Engl J Med 2005;352: 2589-97.
8. Douillard JY, Rosell R, De Lena M, Carpagnano F, Ramlau R, Gonzá les-Larriba JL, et al. Adjuvant vinorelbine plus cisplatin versus observation in patients with completely resected stage IB-IIIA non-small-cell lung cancer (Adjuvant Navelbine International Trialist Association [ANITA]): a randomised controlled trial. Lancet Oncol 2006;7:719-27.
9. Pignon JP, Tribodet H, Scagliotti GV, Douillard JY, Shepherd FA, Stephens RJ, et al; LACE Collaborative Group. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
10. Pisters KMW, Le Chevalier T. Adjuvant Chemotherapy in completely resected non-small cell lung cancer. J Clin Oncol 2005, 23:3270-8.
11. Nicastri DG, Wisnivesky JP, Litle VR, Yun J, Chin C, Dembitzer FR, Swanson SJ. Thoracoscopic lobectomy: report on safety, discharge independence, pain, and chemotherapy tolerance. J Thorac Cardiovasc Surg 2008;135:642-7.
12. Petersen RP, Pham D, Burfeind WR, Hanish SI, Toloza EM, Harpole DH Jr, D'Amico TA. Thoracoscopic lobectomy facilitates the delivery of chemotherapy after resection for lung cancer. Ann Thorac Surg 2007;83:1245-9
13. Strauss GM, Herndon JE 2nd, Maddaus MA, Johnstone DW, Johnson EA, Harpole DH, et al. Adjuvant paclitaxel plus carboplatin compared with observation in stage IB non-small-cell lung cancer: CALGB 9633 with the Cancer and Leukemia Group B, Radiation Therapy Oncology Group, and North Central Cancer Treatment Group Study Groups. J Clin Oncol 2008;26:5043-51.
14. Hanna N, Shepherd FA, Fossella FV, Pereira JR, De Marinis F, von Pawel J, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small-cell lung cancer previously treated with chemotherapy. J Clin Oncol 2004;22:1589-97.
15. Raymond E, Chaney SG, Taamma A, Cvitkovic E. Oxaliplatin: a review of preclinical and clinical studies. Ann Oncol 1998;9:1053-71.
16. Raymond E, Louvet C, Tournigand C, Coudray AM, Faivre S, De Gramont A, Gespach C. Pemetrexed disodium combined with oxaliplatin, SN38, or 5-fluorouracil, based on the quantitation of drug interactions in human HT29 colon cancer cells. Int J Oncol 2002;21:361-7.
17. Misset JL, Gamelin E, Campone M, Delaloge S, Latz JE, Bozec L, Fumoleau P. Phase I and pharmacokinetic study of the multitargeted antifolate pemetrexed in combination with oxaliplatin in patients with advanced solid tumors. Ann Oncol 2004;15:1123-9.
18. Scagliotti GV, Kortsik C, Dark GG, Price A, Manegold C, Rosell R, et al. Pemetrexed combined with oxaliplatin or carboplatin as first-line treatment in advanced non-small cell lung cancer: a multicenter, randomized, phase II trial. Clin Cancer Res 2005;11:690-6.
19. Simon R. Optimal two-stage designs for phase II clinical trials. Control Clin Trials. 1989;10:1-10.
20. Smith TJ, Khatcheressian J, Lyman GH, Ozer H, Armitage JO, Balducci L, et al. 2006 update of recommendations for the use of white blood cell growth factors: an evidence-based clinical practice guideline. J Clin Oncol 2006;24:3187-205.
21. He J, Yang Y, Chen M. Lobectomy by video-assisted thoracoscopic surgery. Zhonghua Wai Ke Za Zhi 1996;34:76-8.
22. Watanabe A, Koyanagi T, Obama T, Ohsawa H, Mawatari T, Takahashi N, et al. Assessment of node dissection for clinical stage I primary lung cancer by VATS. Eur J Cardiothorac Surg 2005;27:745-52.
23. Junker K. Histopathologic evaluation of mediastinal lymph nodes in lung cancer. Lung Cancer 2004;45 Suppl 2:S79-83.
24. Wittekind C, Compton CC, Greene FL, Sobin LH. TNM residual tumor classification revisited. Cancer 2002;94:2511-6.